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SCIENTIFIC EDITION

JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

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Published by the American Pharmaceutical Association. Publication office: 20th and Northampton Sts., Easton, Pa. Editorial office: 2215 Constitution Ave., Washington, D. C.

Annual Subscription: Journal of the American Pharmaceutical Association, complete $5.00; Canada, $6.00; Other Foreign, $6.50. (a) Scientific Edition, $4.00; Canada, $4.35; Other Foreign, $4.50; Single Numbers, $0.35; Canada, $0.40; Other Foreign, $0.50. (b) Practical Pharmacy Edition, $1.50; Canada, $1.70; Other Foreign, $2.00; Single Numbers, $0.15; Canada, $0.20; Other Foreign, $0.25.

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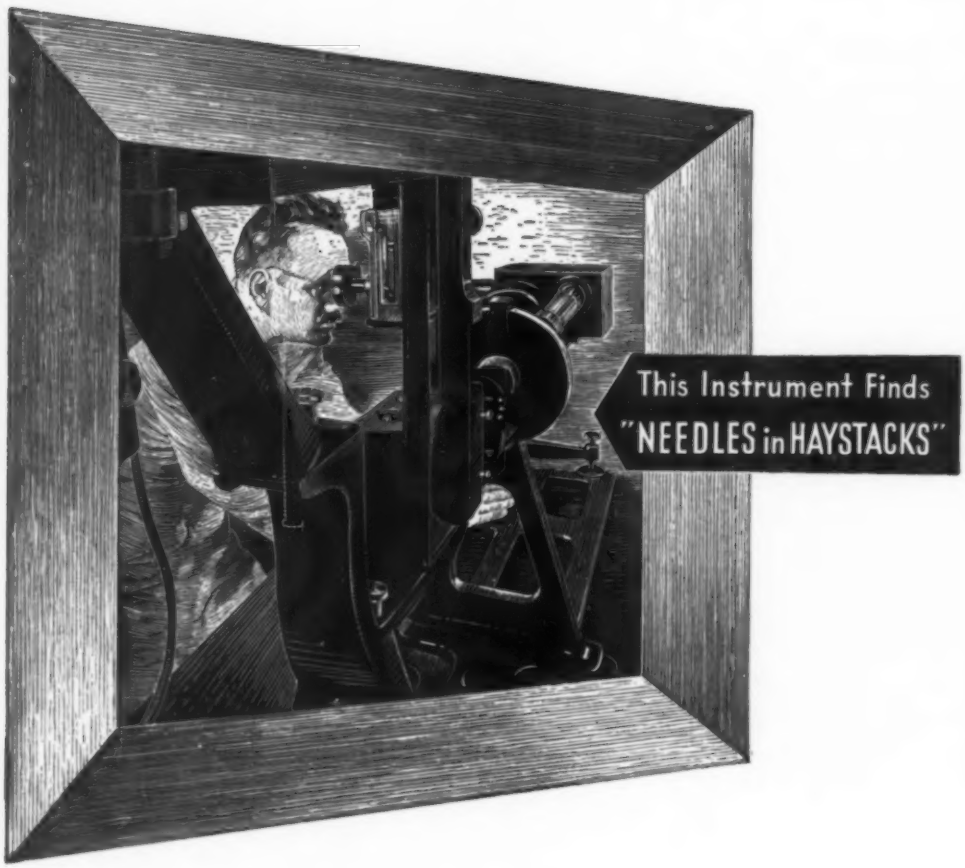
Entered as second-class matter January 23, 1917, at the Post Office at Easton, Pa., under the act of March 3, 1879, as 24 times a year: Scientific Edition monthly on the fifth. Practical Pharmacy Edition monthly on the 20th. Acceptance for mailing at a special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized July 10, 1918.

Vol. XXXI, No. 12 **DECEMBER, 1942**



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Scientific Edition

JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

JUSTIN L. POWERS, EDITOR, WASHINGTON, D. C.

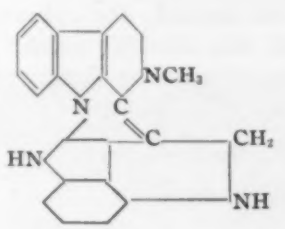
VOLUME XXXI | *DECEMBER, 1942* | NUMBER 12 CONSECUTIVE NO. 23

The Action of Calycanthine*

By A. Ling Chen, Clarence E. Powell and K. K. Chen†

The seeds of *Calycanthus glaucus*, or colloquially "bubby," have been a source of poisoning to cattle and sheep in the Tennessee Valley. Eccles (1) was the first to isolate from the seeds an alkaloid named calycanthine although he did not give the melting point or any analytical data. Wiley (2) made a chemical examination, but added very little information to the subject. Characterization of calycanthine was achieved by Gordin (3) who proposed the empirical formula $C_{11}H_{14}N_2$. Interestingly, the same author obtained isocalycanthine from a second lot of the seeds of *Calycanthus glaucus* (4, 5). Späth and Stroh (6) revised Gordin's empirical formula to $C_{22}H_{28}N_4$ by doubling.

Manske, in a series of brilliant investigations (7, 8, 9, 10), isolated calycanthine from *Calycanthus floridus* and *Meratia praecox*, arrived at the correct empirical formula $C_{22}H_{26}N_4$, and advocated the following structural formula:



It should be noted that the molecule of calycanthine has two tryptamine nuclei, one being reduced. Manske has also isolated calycanthine from *Calycanthus glaucus* and *C. occidentalis*, and observed that Gordin's isocalycanthine is a physical isomer of calycanthine because recrystallization or inoculation gives rise to calycanthine at once (private communication).

An attempt to solve the structure of calycanthine was undertaken by Barger and his associates prior to his death (11). From the seeds of *C. floridus*, Barger, Jacob and Madinaveitia (12) succeeded in isolating a new alkaloid called calycanthidine, $C_{13}H_{16}N_2$. Recently, Manske (13) obtained cocositol, $C_6H_{12}O_6$, an optical isomer of inositol, from the leaves of *C. floridus* and *C. glaucus*.

The plant *Meratia praecox*, from which Manske (7) isolated calycanthine, has been

* Received July 9, 1942, from the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Ind.

† The authors are indebted to Messrs. Charles L. Rose, Robert C. Anderson, E. Brown Robbins and Francis Henderson for their valuable assistance in several of the experiments.

widely cultivated in China. The native name is "La Mei." It is so closely related to the *Calycanthus* species that it has been identified by some authorities as *Calycanthus praecox* (14). It blossoms in midwinter, namely, January. Its fragrant flowers, strung on a thin wire, are often worn by women as hair ornaments. They are also used in medicine as a cooling and sialagogue remedy. Apparently the Chinese have not recognized the toxic properties of its seeds since no mention of them has been made in literature.

Cushny (15) conducted a pharmacologic study of calycanthine, chiefly on its acute toxicity and the cardiac depressant action. McGuigan and von Hess (16) concluded that isocalycanthine and calycanthine had an identical effect in animals.

Dr. Richard H. F. Manske, National Research Laboratories, Ottawa, Canada, provided us with a generous supply of calycanthine in the form of hydrochloride. It was proposed to extend the pharmacologic studies with this alkaloid, which had been so admirably initiated by Cushny (15).

EXPERIMENTAL

Calycanthine hydrochloride is easily soluble in water. A 1–5% solution foams readily upon shaking, but it does not hemolyze the rabbit's erythrocytes in various concentrations from 1:100,000 to 1:100.

1. Acute Toxicity.—By intravenous injection, the median lethal doses were determined in mice and rats as shown in Table I. The alkaloid is more than twice as toxic to rats as to mice. Lethal doses were followed, immediately or within 10–15 min., by a series of clonic convulsions, then succeeded by tonic convulsions. Death usually occurred in from $^1/_2$ to 3 hrs.

Calycanthine hydrochloride appears to be even more toxic to larger laboratory animals such as rabbits. Doses varying from 10 to 40 mg./Kg. were invariably fatal. The maximal tolerated dose was 7.5 mg./Kg. A total of 16 rabbits was employed. Restlessness, tonic convulsions, cyanosis and twitching of the legs preceded death. The animal was often in an opisthotonos position during convulsions.

TABLE I.—ACUTE TOXICITY OF CALYCANTHINE HCl

Animal	Dose, Mg./Kg.	Number Died / Number Injected	Median Lethal Dose ± Standard Error, Mg./Kg.
Mice	30	0/10	43.79 ± 1.89
	34	0/8	
	40	4/10	
	50	7/8	
	60	9/10	
	70	5/5	
Rats	13	1/10	17.16 ± 0.82
	16	2/10	
	20	8/9	

"Sodium Amytal" (Sodium Iso-amyl Ethyl Barbiturate, Lilly) intraperitoneally injected prior to calycanthine afforded a very slight protection. For example, calycanthine alone in a separate test killed all of 5 mice in the amount of 40 mg./Kg. The same dose following the barbiturate killed 6 out of 8 mice. The antidotal action of "Sodium Amytal" is therefore negligible if it is compared with that against strychnine (17), coriamyrtin and picrotoxin (18) and tutin (19). Cushny (15) believed that calycanthine affected a higher part of the central axis primarily. In the light of present findings, the alkaloid probably acts on a center higher than the medulla since "Sodium Amytal" is most effective in detoxifying poisons that act on the medulla and spinal cord.

In frogs calycanthine hydrochloride in doses of 0.2, 0.5 and 1 mg./Gm., injected into the lymph sac, caused gradual depression and prostration. The animal lay flat on its abdomen after a lapse of an hour or longer. When placed in a new position, its hindlegs often stretched out, toes twitched and the head retracted. At no time was there occurrence of typical spasms or convulsions. The ventricle stopped at diastole $4^1/_2$ to 6 hrs. after the administration of the largest dose, namely, 1 mg./Gm. Injection of 0.1 mg./Gm. did not appear to affect the frog.

The reaction of frogs to toxic doses of calycanthine is thus one of depression, while that of mice, rats and rabbits is certainly one of stimulation. This contrast of response between warm-blooded animals, on the one hand, and cold-blooded animals as represented by frogs, on the other, is probably comparable to what was previously observed with sodium 1:3-dimethylbutylethyl-barbiturate (20).

2. Blood Sugar and Count.—Two of the 3 rabbits were injected intravenously with 7.5 mg. of calycanthine hydrochloride per Kg. of body weight; and one, 5 mg. per Kg. At various intervals, but more frequently during the first hour, their blood sugar was determined according to the procedure of Hagedorn and Jensen (21), and their erythrocytes and leucocytes, including the differential, were counted by the usual methods. Hyperglycemia definitely occurred as shown in Fig. 1. The results in the other rabbits were confirmatory. The changes in blood counts were slight and all within normal limits of variation.

3. Circulation.—Just as Cushny (15) reported, calycanthine was found to produce a fall of arterial blood pressure in anesthetized animals. The average effective dose in cats was 10–20 mg., and that in dogs. 40–60 mg. There was a slight decrease in heart rate with an increase in amplitude of respira-

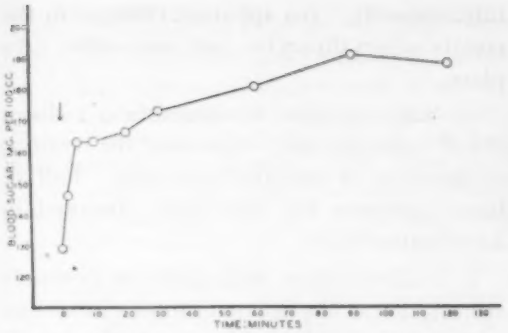


Fig. 1.—Action of calycanthine on blood sugar.

Rabbit, female, weighing 2.05 Kg., was given intravenously (at arrow) 7.5 mg. of calycanthine HCl/Kg. of body weight. Note the increase of blood sugar.

tion during the fall of carotid blood pressure. Atropinization did not nullify the depressor action. Recovery was prompt—a matter of 3–10 min.

There was a definite depression of the ventricular contraction under the influence of calycanthine. Figure 2 shows a myocardiographic tracing of a cat recorded with a dose of 10 mg. It is closely comparable to the one published by McGuigan and von Hess (16) on isocalycanthine.

4. Isolated Intestines and Uteri.—Stimulation resulted upon the addition of calycanthine hydrochloride on the isolated rabbit's intestines and uterus. Examples are given in Fig. 3. Ergotoxine ethanesulfonate did not antagonize the effect on the uterus, so that the action was not due to sympathetic

Fig. 2.—Action of calycanthine on mammalian heart.

Cat, female, weighing 2.817 Kg., was decerebrated and pithed, under artificial respiration with an open chest. The myocardiogram of the right ventricle was recorded. At arrow, a dose of 10 mg. of calycanthine HCl was injected by the femoral vein. The decrease in amplitude of contractions is obvious—with rapid recovery.

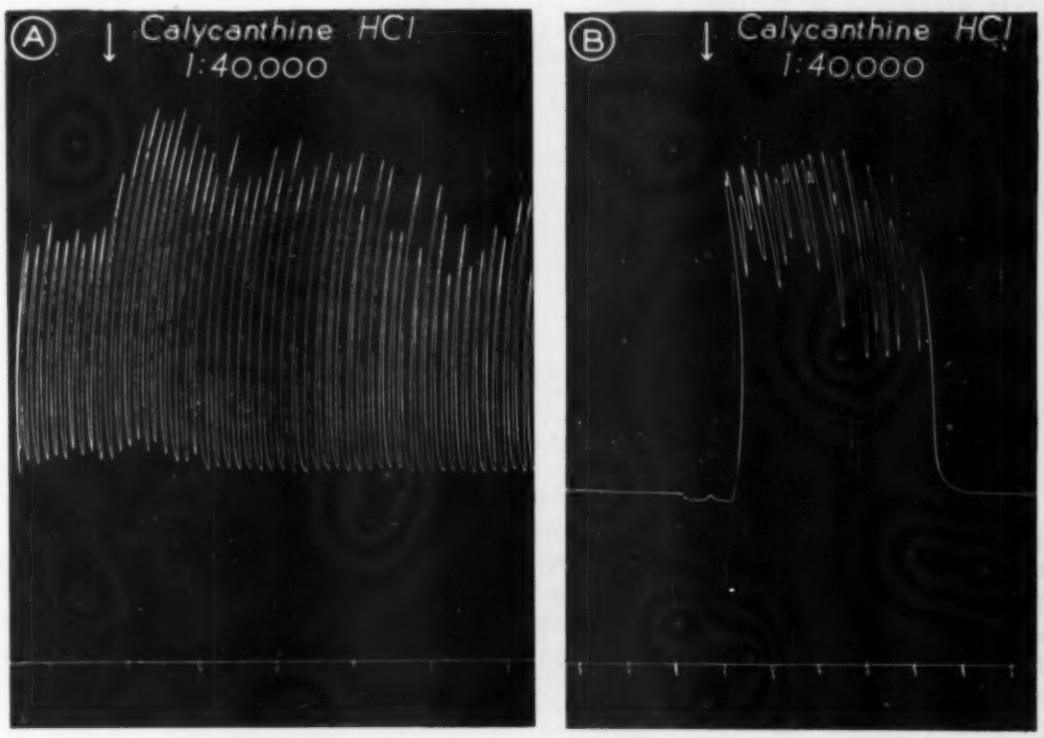


Fig. 3.—Action of calycanthine on isolated smooth muscle organs.

A.—A strip of isolated rabbit's intestine, immersed in Tyrode's solution at 38° C., was stimulated by calycanthine HCl in the concentration of 1:40,000.

B.—A strip of isolated rabbit's uterus, immersed in Tyrode's solution, was contracted by calycanthine HCl in the same concentration.

stimulation. Calycanthine caused a very feeble contraction of the isolated guinea pig's uterus in the concentration of 1:10,000.

SUMMARY

1. The acute toxicity of calycanthine hydrochloride has been determined in mice, rats, rabbits and frogs. Toxic doses cause stimulation in the first three species of animals, but depression and prostration in frogs.

2. Calycanthine hydrochloride induces hyperglycemia in rabbits when injected intravenously. No apparent changes in the counts of erythrocytes and leucocytes take place.

3. Calycanthine hydrochloride reduces blood pressure and depresses the cardiac contraction in anesthetized cats. Fall of blood pressure has also been observed in anesthetized dogs.

4. Calycanthine hydrochloride produces stimulation of the isolated rabbit's intestines and uterus. It has only slight effect upon the isolated guinea pig's uterus.

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Ketone Alcohols*,†

I. Derivatives of 2-Methyl-pentanol-2-one-4

By Clifton Eugene Miller‡

It was reported in a previous paper (1) that preliminary pharmacological tests indicated that the dibromoureide of 2-methyl-pentanol-2-one-4 (diacetone alcohol) possessed hypnotic action. It seemed of interest therefore to prepare other derivatives and to determine, if possible, whether the degree of hypnosis might be increased or diminished by the substitution of various groups or atoms. This paper presents an introductory report on the preparation of certain acetyl, chlorine, nitrogen and sulfur derivatives of 2-methyl-pentanol-2-one-4.

* A contribution from the Department of Pharmaceutical Chemistry, North Dakota Agricultural College, Fargo, N. D.

† Presented to the Scientific Section of the A. PH. A., Detroit meeting, 1941.

‡ Professor of Pharmaceutical Chemistry, School of Pharmacy, North Dakota Agricultural College.

EXPERIMENTAL

Preparation of 2-Methyl-2-chloro-pentanone-4.—One mole of 2-methyl-pentanol-2-one-4 and three moles of hydrochloric acid, sp. gr. 1.175, were placed

in a liter separatory funnel and shaken vigorously for 15 min. following the method of Norris (2). The mixture became hot and rapidly assumed a dark red color. The addition of calcium chloride caused two separate layers to be formed. The lower one, which consisted chiefly of water, hydrochloric acid and some acetone, was discarded. The upper layer was carefully washed with a saturated solution of sodium carbonate until neutral to litmus and then dried over anhydrous sodium sulfate. The dried product was distilled in vacuum and the fraction boiling at 45–47° C./25 mm. was collected. This distillate was colorless, had an aromatic odor and gave a positive halogen test. A peculiar phenomenon observed repeatedly at this point was the rapid darkening in the color of the liquid to a deep brownish red. This darkened product possessed a sp. gr. of 0.9712 at 15° C.; $n^{20°} = 1.4340$; was insoluble in water and did not react with phenyl isocyanide. A small amount of this product agitated with water gave a positive test for halogen showing possibly a partial hydrolysis in contact with water. Several attempts to remove this brownish red color failed.

Preparation of the Amine of 2-Methyl-2-chloropentanone-4.—A mixture of 21 Gm. of potassium phthalamide (3) and 30 Gm. of 2-methyl-2-chloropentanone-4 was placed in a 500-cc. flask and heated on an oil bath to gentle refluxing for a period of 10 hrs. The mixture gradually solidified after which the solid material was then taken up in 850 cc. of 98% alcohol and refluxed for half an hour on a water bath. The alcoholic liquid which assumed a reddish yellow color was evaporated under reduced pressure and yielded tan-colored crystals melting at 228° C. Repeated recrystallization from dilute alcohol raised the melting point to 234° C. This product upon treatment with carbon disulfide did not yield a residue upon evaporation of the solvent. The nearly colorless crystals mixed with phthalamide melted at 234° C. It is believed, therefore, following the method just outlined, that at present the formation of an amine is not possible.

Preparation of 2-Methyl-2-acetyl-pentanone-4.—Fifty grams of acetyl chloride was added by means of a dropping funnel to 62 Gm. of 2-methyl-pentanol-2-one-4 and the mixture was warmed to about 80° C. on a water bath to start the reaction. Hydrochloric acid gas was given off and a noticeable darkening in color occurred. The resultant mixture was treated with saturated sodium carbonate solution until neutral to litmus, whereupon the upper layer which separated was dried over calcium chloride and then distilled. The physical properties and boiling points are given in the following table.

TABLE I

Tube	B. P., ° C.	Color	Odor
1	44–47/17 mm.	Dark	Sharp
2	44–47/14 mm.	None	Faint
3	50–52/14 mm.	None	Sweet

The distillates of tubes 2 and 3 were combined and redistilled. The fraction boiling at 46–47° C./15 mm. possessed a sweet odor, sp. gr. of 0.9332 at 15° C., and was insoluble in water. A 1.8916-Gm. sample required 0.676 Gm. of KOH for saponification; whereas, calculated for $C_8H_{14}O_2$, 0.671 Gm. of KOH is required.

Preparation of the Thiol Analogue of 2-Methyl-pentanol-2-one-4.—Various methods for the linking of sulfur to carbon are available (4). A survey of these methods and others which presented themselves was carried out in search of a suitable method for introducing atomic sulfur to a carbon chain by the breaking of a C=O group.

The Use of H_2S.—Fifty cubic centimeters of 2-methyl-pentanol-2-one-4 was saturated with hydrogen sulfide until the liquid was light yellow in color. The resultant mixture was then heated to 80° C. on a water bath until the odor of hydrogen sulfide had disappeared and then allowed to cool to room temperature, filtered and poured into a saturated sodium sulfite solution. After vigorous shaking the mixture was filtered, allowed to separate into two layers and the aqueous layer discarded. Distillation of this upper layer showed the product to be a mixture. The fraction boiling at 36–42° C./18 mm. gave a qualitative test for sulfur.

The Use of H_2S and $CaCl_2$.—In the hope of obtaining more definite results, the above process was repeated with the addition of 10 Gm. of $CaCl_2$ as a dehydrating agent. This method was discontinued because poor yields were obtained.

The Use of Sulfurated Potash.—Fifty grams of sulfurated potash, calculated as K_2S_3, was washed once with 95% alcohol and filtered with suction. This moist residue was placed in a 500-cc. flask and a mixture of 50 cc. of benzene and 100 cc. of 2-methyl-pentanol-2-one-4 added. The mixture was then heated under reflux on an electric plate for 6 hrs., during which time the solution gradually darkened to a chocolate-brown, and a gas was evolved. The resulting solution was allowed to cool to room temperature, filtered and the filtrate placed in a salt-ice bath to insure complete precipitation of sulfur. After filtering a second time the liquid was subjected to fractional vacuum distillation to remove benzene and acetone which were discarded.

The high-boiling fraction upon redistillation yielded 40 cc. of a faintly yellow liquid boiling at 70–72° C./22 mm. This liquid had a sp. gr. of 0.9441 at 15° C.; $n^{20°} = 1.4247$; was found to be miscible with water, contained at least one double bond inasmuch as it rapidly decolorized a chloroform solution of bromine. The product gave a positive sodium nitroprusside test for sulfur. Degradation with potassium hydroxide and heat yielded acetone, sulfur and possibly isopropyl mercaptan. Further investigation on this product is being carried out and will be reported in a future paper.

CONCLUSIONS

1. Several derivatives of 2-methyl-pentanol-2-one-4 have been prepared and some of their physical properties noted.

2. Efforts to form the amine of 2-methyl-2-chloro-pentanone-4 have thus far been unsuccessful.

3. Some preliminary work on the introduction of sulfur into 2-methyl-pentanol-2-one-4 has been completed.

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Ketone Alcohols*,†

II. Derivatives of the Polymerization of Pentanone-3

By Kathryn C. Odney and Clifton E. Miller‡

Certain derivatives of 2-methyl-pentanol-2-one-4 have been prepared (1). The pharmacological action shown by one of these derivatives made it seem worth while to prepare higher homologues, confining our efforts to the even-numbered carbon atom compounds, with the intention of determining the effect of length of carbon chain on the pharmacological action of ketone alcohols. The authors present a report of the work completed thus far on the polymerization of pentanone-3 to form 3-ethyl-octanol-3-one-6.

EXPERIMENTAL

The pentanone-3 employed in this investigation was prepared by the following methods: oxidation of diethyl carbinol by the use of Beckman's oxidizing mixture, employing variable amounts of benzene as a carrying agent; consistently small yields were obtained following this procedure, therefore method two consisting of the dry distillation of calcium propionate was employed with favorable results.

The polymerization of pentanone-3 was accomplished by placing 200 cc. of pure ketone in a 500-cc. three-neck flask fitted with a Soxhlet extractor containing a thimble of barium hydroxide, a thermometer for recording internal temperature and a device for removal of samples. It was found advantageous to place two long water-cooled condensers above the Soxhlet extractor to minimize the amount of loss by volatilization. Heating, with a flask temperature of 110–115° C., was continued for a period of 100 hrs. during which time the mixture became dark in color and samples were withdrawn at varying intervals for refractive index determinations. The results are summarized in the following table. All readings were made at 20°C.

TABLE I

Hours of Heating	Average Reading	Hours of Heating	Average Reading
0	1.3929	50	1.3947
5	1.3937	60	1.3948
15	1.3937	70	1.3943
20	1.3940	80	1.3951
30	1.3940	90	1.3943
40	1.3940	100	1.3948

It was apparent from the results obtained that a complete polymerization did not occur and this is in accord with the published results of Voitila (2) who found incomplete polymerization of methyl-ethyl ketone under similar conditions. A possible explanation of the oscillation in readings may be that when the samples were withdrawn from time to time the ratio between the polymerized and unpolymerized products was not always the same.

After completing this heating period, the product was allowed to cool to room temperature and filtered.

* From the Department of Pharmaceutical Chemistry, North Dakota Agricultural College, Fargo, N. D.

† Presented to the Scientific Section of the A. PH. A., Detroit Meeting, 1941.

‡ Professor of Pharmaceutical Chemistry, School of Pharmacy, North Dakota Agricultural College.

The filtrate was distilled in vacuum and the portion boiling at 24 °C./27 mm. collected. A total of 55 Gm., representing a yield of 34%, was obtained. This product which was colorless and very volatile had a boiling point of 98° C. when determined by micro methods

This volatile liquid yielded a phenylurethane melting at 232–233° C.; an α-naphthylurethane melting at 217° C.; and a dinitro-osazone consisting of bright yellowish orange crystals melting at 148° C. No color was observed on the addition of a small amount of this product to anhydrous copper sulfate. Schiff's reagent gave a negative reaction.

Because of its extreme volatility, only an approximate specific gravity was determined between the range of 0.84–0.86 at 15° C. The product rapidly decolorized a solution of bromine in chloroform leading us to suspect the presence of an unsaturated structure. Several iodine determinations were carried out with values ranging from 91 to 139. This variance may be attributed, possibly, to the extreme volatility of the liquid.

CONCLUSIONS

1. Preliminary studies of the polymerization of pentanone-3, using barium hydroxide as the condensing agent have been made.

2. The principal product formed appeared to be an unsaturated aliphatic alcohol of low molecular weight.

3. The failure to isolate the desired 3-ethyl-octanol-3-one-6 is being investigated.

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The Phytochemistry of Helonias

I. Preliminary Examination of the Drug*

By E. L. Cataline and D. E. Francke†

Chamælirium luteum (L.) A. Gray, is a perennial, dicœcious herb of the lily family found growing in low grounds from New England to Georgia and westward. It is known by such synonyms as False Unicorn, Blazing Star, Starwort, Devil's Bit and Helonias, the last named being the title by which the dried rhizome and roots are recognized by the National Formulary. The drug has long been recognized by the Homeopathic Pharmacopœia of the United States, and it was used as a remedy by the American Indians (1, 2, 3).

Moser (3) has reported on the pharmacognosy of the drug, but chemical investigation is apparently limited to the work of Greene and Kruskal[1]. Greene (4, 5) reported the presence of a saponaceous glycoside, reducing sugar, tannic acid and a small quantity of a white substance which he did not characterize but believed to be a fatty acid. He further showed that the glycoside was hydrolyzed when heated with 2% hydrochloric acid, the products of the hydrolysis being a reducing sugar and a white, resinous substance which he named chamæliretin. Ultimate analyses carried out by Kruskal (6) indicated that the empirical formula of the glycoside may be represented as $C_{18}H_{32}O_9$ or $C_{36}H_{62}O_{18}$.

Helonias has been used as a sialagogue, emetic and uterine tonic. In connection with the latter use it is of interest to note that Pilcher (7) has shown that the drug has no action on the excised uterus of the guinea pig.

* Received June 11, 1942, from the University of Michigan, College of Pharmacy, Ann Arbor, Mich.

† Assistant Chief Pharmacist, University of Michigan Hospital and student in the Horace H. Rackham School of Graduate Studies, University of Michigan.

[1] In a paper published subsequent to the completion of this paper, Marker [*J. Am. Chem. Soc.*, 64 (1942), 1238] showed that diosgenin could be isolated from *Chamaelirium luteum*.

EXPERIMENTAL

PRELIMINARY EXAMINATION

The moisture content, determined by heating at 100° C. to constant weight, was found to be 10.8%. Using the U. S. P. methods, the total ash was found to be 4.33% and acid-insoluble ash was 1.58%. No

volatile oil was found by the method of Clevenger (8). No alkaloid could be detected by the Stas-Otto method (9) or by the method for ether soluble alkaloids (10).

THE GENERAL METHOD

Two 500-Gm. samples of the drug[1] were subjected to the action of a series of solvents. The percentage of the drug extracted by each solvent is shown in the following table:

Solvent	Per Cent
Petroleum benzin (b. p. 60–75° C.)	2.1
Diethyl ether	1.8
Chloroform	1.1
Alcohol	17.8
Water	14.1
Sulfuric acid (1.25%)	16.0[a]
Sodium hydroxide (1.25%)	25.3[a]
Total extractive	78.2

[a] The weight of reagent used was subtracted from the weight of extractive.

PETROLEUM BENZIN EXTRACT

The petroleum benzin extract was a dark green, viscous oil. The presence of glycerol was indicated by the production of vapors of acrolein when a small quantity of the oil was heated with potassium bisulfate (9). The Elaidin Reaction (9) was positive indicating the presence of oleic acid. A thin layer of the oil, spread on a glass plate became only slightly more viscous after standing in air for 3 weeks. This was taken to indicate that the more highly unsaturated acids were present only in small amounts, if at all.

The oil was found to possess the following constants:

Specific gravity, 20° C.	0.9456
Refractive index, 25° C.	1.4742
Saponification value	193.8
Iodine value	76.2

Unsaponifiable Matter.—The unsaponifiable matter, determined by the modified Kerr-Sober method (11), constituted 10% of the petroleum benzin extract. It was a very viscous, light brown, oily substance which responded to the usual color reactions for sterols (12). An ether solution absorbed bromine. No crystalline material could be isolated from the unsaponifiable matter when it was heated with acetic anhydride or benzoyl chloride. Attempts to fractionate the mixture by means of alcohol were unsuccessful.

Liquid and Solid Fatty Acids.—Because of the relatively small quantity of the oil available, no attempt was made to fractionate the liquid and solid fatty acids quantitatively. A quantity of the oil was saponified, the unsaponfiable matter removed by shaking with ether, and the liquid and solid fatty acids separated by the lead salt-ether method (11). The percentages of the liquid and solid fatty acids were approximately 60% and 30%, respectively.

The liquid fraction was oxidized with potassium permanganate at 0° C. (13), the reaction mixture filtered and the hydroxy acids precipitated by acidification. The major portion of the precipitate consisted of 9,10-dihydroxystearic acid, m. p. 132–133° C. after recrystallization from alcohol. When it was mixed with an authentic sample of 9,10-dihydroxystearic acid prepared from oleic acid by the same process there was no depression of the melting point.

The remainder of the precipitate was recrystallized from water and then several times from alcohol, m. p. 174–175° C. This acid is undoubtedly the "high-melting" tetrahydroxystearic acid (11, 13). No hexahydroxystearic acid could be isolated by this method. Attempts to brominate the liquid fatty acid mixture yielded virtually no ether-insoluble material. It appears, therefore, that the oil contains very little, if any, linolenic acid (13).

Fractionation of the solid fatty acids using magnesium acetate yielded inconclusive results. One-tenth the quantity of magnesium acetate required to precipitate the solid fatty acids completely was added to a hot alcohol solution of the acids. After the mixture had cooled, the precipitate was filtered off, air dried, suspended in ether and decomposed with dilute hydrochloric acid. The ether layer was separated, dried, the solvent removed, and the residue recrystallized from alcohol. After neutralization of the filtrate with ammonium hydroxide the process was repeated. In some instances no precipitate was obtained and another addition of magnesium acetate was necessary. By this process five fractions were obtained.

The residue from the first precipitation was gummy and no crystalline material could be isolated from it. The second fraction was crystalline and melted at 70.5° C. When mixed with an authentic sample of stearic acid there was no depression of the melting point. The remaining fractions did not exhibit sharp melting points. Fractions 3 and 4 melted at 55–57° C. and were undoubtedly mixtures. Fraction 5 melted over a much wider range.

OTHER EXTRACTS

Diethyl Ether Extract.—The diethyl ether extract consisted of a brown, semisolid, resinous substance. It was completely soluble in potassium hydroxide solution but only partially soluble in alcohol. No crystalline material could be isolated from it upon extraction with a number of solvents.

No color developed when an aqueous extract of the resinous material was treated with ferric chloride T. S. indicating the absence of gallic acid.

Chloroform Extract.—The chloroform extract was similar in appearance and behavior to the diethyl ether extract.

Alcohol Extract.—The alcohol extract was obtained as a black, sticky semisolid. A foam was produced when a portion was shaken with water. The aqueous layer did not yield a color with ferric chloride T. S.

[1] Purchased from the S. B. Penick Company. Labeled "Granulated."

Work upon this fraction, which contains the saponaceous glycoside, will be reported in detail later.

Water Extract.—The water extract was a brown, granular solid. An aqueous solution of the substance foamed when shaken. The presence of reducing substances was indicated by the production of cuprous oxide upon boiling with Fehling's solution. The ferric chloride test was negative. A deep blue color was produced when a solution of iodine in potassium iodide was added to an aqueous solution of the extract.

SUMMARY

A preliminary chemical investigation of the rhizome and roots of Helonias (*Chamælirium luteum* A. Gray) is reported. No volatile oil or alkaloid could be detected. The nondrying, fixed oil was shown to contain oleic, linoleic and stearic acids. The presence of other saturated fatty acids and sterols was indicated. No tannic or gallic acid could be detected.

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Comparative Stability of Vitamin A in Cod-Liver Oil and in Oleovitamin A and D*

By Arthur D. Holmes and Madeleine G. Pigott

When it was foreseen that the supply of cod-liver oil would not be adequate for the country's needs, the Revision Committee of the United States Pharmacopœia provided for a substitute product which would possess the same vitamin A and vitamin D value as official cod-liver oil and designated it oleovitamin A and D. The official specifications (1) for this product provide that natural vitamin A and vitamin D may be dissolved in edible vegetable oils and the mixture shall have a U. S. P. vitamin potency of not less that 850 but no more than 1100 vitamin A, and not less than 85 and no more than 110 vitamin D units per gram. Obviously oleovitamin A and D does not contain any iodine (2), arsenic (3) or other substances which are found in cod-liver oil and its therapeutic value resides wholly in its vitamin content.

In the commercial distribution of oleovitamin A and D, this material, like other pharmaceutical products, is likely to remain in the hands of the wholesaler or upon the druggist's shelf for indefinite periods. Therefore a question naturally arises as to the relative permanency of the fat-soluble vitamins as they naturally occur in cod-liver oil and in solution in vegetable oils. Earlier studies in this laboratory have shown that the permanency (4) of vitamin A in cod-liver oil is influenced by the exposure of the oil to light. In other words, the rate of destruction of vitamin A in cod-liver oil packed in Flint glass containers depends upon both the intensity of the light or direct sunshine and the length of time that the oil is exposed to it. Accordingly, it seemed of inter-

* Received October 29, 1942, from the Research Laboratories, The E. L. Patch Company, Stoneham, Mass.

est to compare the permanency of vitamin A in natural cod-liver oil and in oleovitamin A and D when stored under identical conditions.

EXPERIMENTAL

The cod-liver oils were medicinal cod-liver oils taken from stock and were believed to be typical of commercial cod-liver oil. One oil sample, No. 4, had a vitamin A potency of approximately 1000 U. S. P. vitamin A units and sample 5 had a potency of approximately 4000 U. S. P. vitamin A units/Gm. Sample 4 was chosen because its potency was essentially the same as that specified for oleovitamin A and D. While medicinal cod-liver oils with a vitamin A potency of 4000 units/Gm. are not common, sample 5 was selected as representing cod-liver oils of high vitamin A potency.

The oleovitamin A and D oils, samples 1, 2 and 3, were prepared by dissolving a vitamin A concentrate in edible cottonseed, peanut and corn oils, respectively. The three vegetable oils were subjected to the vitameter assay procedure and all were apparently free from substances which would influence the vitameter assays of oleovitamin A and D oils prepared with the vegetable oils as diluents. Vitamin A concentrate designated as "winterized" was obtained from the Distillation Products Company. It was prepared by molecular distillation from natural sources and had a potency of 200,000 vitamin A units/Gm. To eliminate any possible destruction of vitamin A during the preparation of the oleovitamin A and D samples, the vitamin A concentrate was mixed with the vegetable oils while in direct contact with nitrogen.

Since Flint glass bottles are frequently used for distributing cod-liver oil, it was decided to package the samples of cod-liver oil and the oleovitamin A and D in 2-oz. Flint glass bottles with screw cap closures. The samples were placed in direct sunshine on the southwest side of the building. The daytime temperature of the atmosphere surrounding the samples was approximately 86° F. During the night the temperature dropped to approximately 50° F. The five samples were stored under these conditions for a period of 11 days during the last of November and first of December. Of this time between 4 and 5 days were cloudy or raining and the samples were exposed to only skyshine. In other words, the samples were exposed to early winter sunshine for something over 6 days. This exposure to light was somewhat similar to but very much more severe than that to which cod-liver oil and oleovitamin A and D products might be exposed in drugstores. At the end of this time there had been a noticeable fading of the characteristic cod-liver oil color of the cod-liver oil samples. The color of the oleovitamin samples was also less intense than at the beginning of the period of exposure.

Attention was centered upon vitamin A since it is very generally believed that vitamin A is less stable than vitamin D. The vitamin A potencies of the cod-liver oils and of the mixtures of edible oils and vitamins were determined with the Hilger vitameter. The assay samples were dissolved in isopropyl alcohol. A specially purified, 99% isopropyl alcohol was used. The vitameter readings were made within 15 min. or so after the samples were prepared. These readings were expressed as *E* values (extinction coefficient). The results of the vitameter assays at the beginning of the experiment, at the end of the experiment, the decrease in the *E* values during the period of exposure and the estimated vitamin potency at the end of the experiment are reported in Table I.

It will be noted that at the start of the exposure of the samples to light the *E* values of the three oleovitamin A and D samples were in close agreement, being 0.526, 0.521 and 0.529, respectively, for the cottonseed, peanut and corn oil mixtures. The vitamin A content of cod-liver oil, sample 4, was slightly higher than that of the oleovitamin oils since it possessed an *E* value of 0.652. The *E* value for sample 5 reported to have a vitamin A potency of 4000 vitamin A units/Gm. was 2.088. After 11 days' exposure to light the vitameter readings for the three oleovitamin A and D oils were 0.101, 0.098 and 0.104 respectively, for the cottonseed, peanut and corn oil, solutions. The vitameter values for the cod-liver oil samples were 0.329 and 1.175.

For purposes of comparison, the decrease in *E* values during the 11 days' exposure are reported on a percentage basis. The decrease in *E* values for the oleovitamin A and D oils were 80.80, 81.19 and 80.34%, respectively, for the cottonseed, peanut and corn oil solutions. The average decrease was 80.8% However, the decrease in the *E* values for the two cod-liver oil samples was definitely less than that of the oleovitamin A and D samples, being 49.55% and 43.73%, respectively, for the samples having reported original potencies of 1000 and 4000 vitamin A

TABLE I.—COMPARATIVE STABILITY OF VITAMIN A IN COD-LIVER OIL AND IN OLEOVITAMIN A AND D

Sample No.	Vitamin A Containing Oils	Vitameter Reading: At Start, *E* Value	Vitameter Reading: After 11 Days' Storage, *E* Value	Decrease During Storage: *E* Values, Per Cent	Decrease During Storage: Vitamin A, U. S. P. Units
1	Oleovitamin A and D (cottonseed oil)	0.526	0.101	80.80	808
2	Oleovitamin A and D (peanut oil)	0.521	0.098	81.19	814
3	Oleovitamin A and D (corn oil)	0.529	0.104	80.34	802
4	Cod-liver oil	0.652	0.329	49.54	375
5	Cod-liver oil	2.088	1.175	43.73	1767

units, respectively. The estimated decrease in vitamin A potency of the oleovitamin A and D oils during the exposure test were practically identical, being 808, 814 and 802 units, respectively, for the cottonseed, peanut and corn oil preparations The decrease in potencies of the cod-liver oils was estimated to be 375 and 1767 units/Gm., respectively, for samples 4 and 5. The difference in the vitamin A loss in the two cod-liver oil samples is doubtless influenced by the marked difference in the vitamin A potency of the samples. However, the average loss of vitamin A, 46.64%, for the cod-liver oil samples is only about half the loss, 80.80%, for the oleovitamin A and D products. Apparently the vitamin A in cod-liver oil is protected to some extent by an antioxidant in the cod-liver oil or it is in a more stable form than that which was dissolved in the vegetable oils.

SUMMARY

Samples of oleovitamin A and D prepared with cottonseed, peanut and corn oils and samples of medicinal cod-liver oils were exposed to early winter sunshine and skyshine for 11 days to compare the permanency of their vitamin A content.

Vitameter assays were made of the vitamin A content of the oleovitamin A and D oils and of the cod-liver oil samples before and after the exposure test. The results of these tests showed that there was approximately 80% loss of the vitamin A content of the oleovitamin A and D, regardless of whether cottonseed, peanut or corn oil was used as a diluent. The loss of vitamin A from the cod-liver oils was only about one-half the vitamin A loss from the oleovitamins. Possibly cod-liver oil may contain some natural antioxidant or its vitamin A content may be in a more stable form than that of the vitamin A concentrate incorporated in the vegetable oils, used for preparing the oleovitamin oils employed in this study.

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Zinc Peroxide*,†

By Roland H. Noel and E. V. Lynn

The substances called zinc peroxide have been known and used in medicine for years. Since Thenard, in 1818, first produced (1) his "deutoxyde de zinc" by the action of zinc hydroxide and hydrogen peroxide, many others have prepared similar materials and by like processes, but almost always to yield products with somewhat differing composition. All of them contained zinc, oxygen and hydrogen in variable proportions, but hardly any two yielded the same results in elementary analysis, and this has been true often in two substances made by almost identical methods. This may perhaps explain the markedly inconsistent results in therapeutic application since introduction into practice 40 years ago. However, more recent reports would seem to indicate that, providing a zinc peroxide is used that is proved to contain maximum activity, excellent results can be obtained in arresting lesions caused by all types of anaerobic organisms.

* From the Department of Chemistry, Massachusetts College of Pharmacy, Boston, Mass.

† Presented to the Scientific Section of the A. PH. A., Detroit meeting, 1941.

EXPERIMENTAL

Because no one here has ever prepared a compound of the formula ZnO_2 or any other peroxide that contained no hydrogen, the present experiments were instituted to learn if such a compound can exist. In an extensive series, pure zinc oxide was subjected to oxygen at temperatures of 100° to 1000° C. but in every case the oxide was found unchanged analytically after treatment, and no evidence of active oxygen could be found in the residue.

The attempt was next made to attain peroxida-

tion by means of nascent oxygen, using the notable instability of silver oxide as the source. Mixtures of this with zinc oxide were subjected to temperatures up to 220° C. at which point samples of silver oxide are all decomposed. In no case, however, was the residue found to contain active oxygen.

The results with ozone were somewhat difficult to interpret. Oxygen containing ample ozone from an ozonizer was passed through zinc oxide at several temperatures up to 100° C. In all cases the residual material liberated no iodine from a solution of potassium iodide, but did so if the solution was acidified, which is characteristic of ozone itself. Also, when talc or lime was employed in place of zinc oxide, the same result was obtained. It would seem that occlusion of the ozone had occurred in all of the powders. This was partly confirmed by the fact that the residue from zinc oxide was found by analysis to contain as great a percentage of zinc as at the start. Furthermore, heat apparently removed the active oxygen at slightly over 100° C.

It was also found that an active material was not produced by interaction of the oxide or chloride of zinc and benzoyl peroxide. The former was shaken with the latter in absolute alcohol, but in no instance was the insoluble residue able to liberate iodine from potassium iodide.

From the results of our experiments, we conclude that a compound corresponding to the name zinc peroxide does not exist at ordinary or higher temperatures. The commercial products so labeled all contain hydrogen and would appear to be physical, or possibly chemical, combinations of hydrated zinc oxide with hydrogen peroxide. The most reliable and efficient of these seems to be "ZPO special medicinal." This has the remarkable property o. being fairly stable up to 140° C. and the manufacturers recommend that it be activated and sterilized by heating at that temperature for 4 hrs. We have found that loss of active oxygen under these circumstances is under 2%.

In applying any commercial material in therapy, we believe that excellent results can be obtained if the product that is employed is found by assay to be sufficiently active. Certainly before any attempt is made to use a given substance, it should be submitted to such an assay. ZPO special medicinal, even after sterilization as directed, gives a value of 6.7% to 7.0% of available oxygen, 10% to 12% of carbonate and 61% to 65% of total zinc. The loss in activity in storage appears to be about 1% per month.

For application the material is best made into an aqueous suspension, the consistency of which may vary in accordance with the condition in which it is to be used. For example, in infections of the oral cavity it may be made into a very thin suspension and used as a mouth wash or gargle, while in wounds it is generally made into a 40% cream or paste, either packed into the recess or applied on sterile gauze.

One of the chief objections to using the material in the past has been the caking of such preparations after an hour or so. After some experimentation we found that this could be almost entirely overcome by incorporating 10% to 15% of sorbitol, or the less efficient mannitol. Suspensions made with sorbitol and 50% ZPO will not cake within 24 hrs. The preparation we recommend is as follows:

Zinc peroxide	40
Sorbitol	15
Tragacanth	1
Ringer's solution, *q. s.*	100

A good substitute can be made by using water in place of Ringer's solution.

Such preparations have been used under our observation in four cases of chronic undermining varicose ulcers with probable anaerobic infection. Although two of them were of long standing, all four ulcers showed marked healing, the pain was much reduced and the prognosis at present writing is very favorable. The peroxide preparation has been used continuously, being replaced by a new dressing every 24 hrs., and in no instance has any caking been observed.

SUMMARY

1. No evidence could be found for the existence of a true zinc peroxide. The commercial articles all contain hydrogen and are probably combinations of zinc oxide and hydrogen peroxide.

2. The substance for medicinal use should be assayed for active oxygen and it should not be called zinc peroxide.

3. The caking of suspensions can be overcome by adding sorbitol or mannitol. Four cases of chronic ulcer were treated by such a preparation with excellent results.

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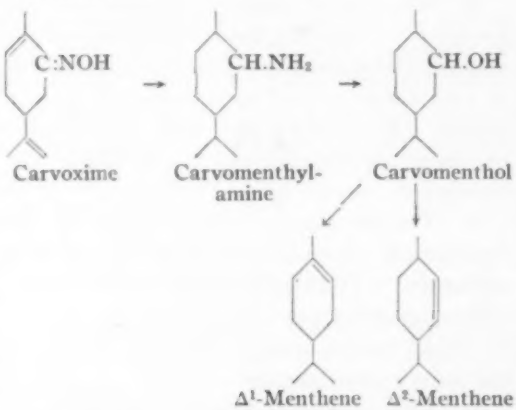
A Chemical Study of the Isomeric Δ^1-Menthenes (Carvomenthenes)*

By Austin A. Dodge† and Edward Kremers‡

The general approach to the *para* menthenes, six isomers of position, has been outlined by Windemuth (1) who also surveyed the literature on the subject. In connection with her experimental work, she reported on derivatives of a menthene (Δ^1-menthene (?)) obtained from a carvomenthol which had resulted upon the reduction of carvacrol. These compounds were optically inactive like their original source, the phenol carvacrol. For a better understanding of the menthenes it seemed desirable to supplement this study by an investigation of the corresponding optically active menthenes. Considerable quantities of both the *d* and *l* modifications of carvoxime were available as products prepared by undergraduate students from *d*- and *l*-carvone, present, respectively, in the volatile oils of caraway and spearmint; these were used as starting materials. Their reduction to carvomenthylamine, its diazotization to carvomenthol, and the dehydration of the latter to carvomenthene, are indicated by the following formulas:



Δ^1-Menthene was first prepared in 1893 by Baeyer (2), who converted limonene to the dihydriodide and thence to carvomenthene, and by Wallach (3), who dehydrated inactive carvomenthol obtained from pinene through a series of reactions.

EXPERIMENTAL

Carvomenthylamine from Carvoxime.—The hydrogenation of the optically isomeric carvoximes over Raney nickel catalyst was performed by James D'Ianni under the direction of Professor Homer Adkins. The maximum temperature attained was 130–140° C.; the pressure range was 2000–3500 lbs. In each case the yield was 66% of the theoretical.

l-Carvoxime yielded *d*-carvomenthylamine, which, in the crude state, had $d^{22°} = 0.8710$ and $[\alpha]_D^{21°} = +7.97°$. The hydrochloride was prepared, and was found to melt at 193–195° C. after recrystallization from water, and at 192–194° C. after recrystallization from an alcohol–ethyl acetate mixture. Read and Johnston (4) report a melting point "above 250°" for a compound prepared from *d*-carvone as a starting material. Wallach (3) reports a melting point of 221–222° C. for an optically inactive compound prepared from pinene through a series of reactions. On the other hand, Wallach (5) found that a compound prepared from *l*-α-phellandrene nitrosite or nitro-α-phellandrene melted at 199–204° C.

The free amine, regenerated from the hydrochloride, distilled at 77–78° C./7 mm. and had $d^{20°} = 0.8617$, $n_D^{23°} = 1.4617$, and $[\alpha]_D^{23°} = +5.92°$. Read and Johnston (4) report b. p. 89.8–90.0° C./16.5 mm., $d_4^{25°} = 0.8505$, $n_D^{25°} = 1.4578$, and $[\alpha]_D^{25°} = +12.47°$.

d-Carvoxime yielded *l*-carvomenthylamine, the hydrochloride of which, after recrystallization from water, melted at 197–198° C. The free amine, regenerated from the hydrochloride, distilled at 81.5–82.0° C./9 mm., and had $d^{21°} = 0.8619$, $n_D^{23°} = 1.4626$, and $[\alpha]_D^{22°} = -8.34°$.

The picrates of the isomeric carvomenthylamines were prepared and recrystallized from alcohol. The melting points of the two compounds were identical, 184–185° C. with decomposition. This derivative has not been previously reported.

The platinic chloride double salts of the respective carvomenthylamines were prepared and analyzed. The *d* compound contained 26.81% of platinum; the *l* compound, 26.50%. Calculated for $(C_{10}H_{19}NH_2.HCl)_2PtCl_4$, the percentage of platinum is 27.095. Wallach (3) reports 26.92%.

Carvomenthol from Carvomenthylamine.—The respective carvomenthylamines, in the form of their hydrochlorides, were converted to the corresponding alcohols by means of the diazo reaction. Equimolecular quantities of the salt and sodium nitrite were

* Abstract of a thesis presented to the Graduate School of the University of Wisconsin in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1941.

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‡ Late Emeritus Professor of Pharmaceutical Chemistry, University of Wisconsin.

used, the reaction mixture being chilled at −3° to −8° C., with either occasional shaking or constant stirring, for about 10 hrs.

Nitrogen was expelled by refluxing the reaction mixture over the steam bath, after which treatment the oily layer was steam distilled. The yield of crude carvomenthol from *d*-carvomenthylamine was 80% of the theoretical; from the *l* form, 92.5%.

Each product was fractionated under high vacuum in an apparatus which was a modification of that described by Bowers (6). The following constants are those of (*a*) the largest and (*b*) the second largest fractions collected:

FROM *d*-CARVOMENTHYLAMINE

Fraction	B. P., °C.	$d^{25°}$	$n_D^{25°}$	$[\alpha]_D^{25°}$
a	43.8–45.5/ 0.03–0.02 mm.	0.9004	1.4630	−1.22°
b	44.0–45.5/ 0.02 mm.	0.9020	1.4645	+1.62°

FROM *l*-CARVOMENTHYLAMINE

Fraction	B. P., °C.	$d^{20°}$	$n_D^{25°}$	$[\alpha]_D^{25°}$
a	40.5–42.5/ 0.025 mm.	0.9050	1.4635	+0.88°
b	42.5–44.5/ 0.025 mm.	0.9079	1.4651	−2.18°

For a product prepared from *d*-carvone as a starting material Johnston and Read (7) report b. p. 101.8–102.0° C./14 mm., $d_4^{13°}$ = 0.9056, $n_D^{17°}$ = 1.4629, and $[\alpha]_D^{13°}$ = +27.69°.

The 3,5-dinitrobenzoate of each of the largest fractions of carvomenthol was prepared; that resulting from the conversion of *d*-carvomenthylamine yielded a product which, after repeated recrystallization from an alcohol–ethyl acetate mixture, melted at 105–106° C., while the derivative of carvomenthol prepared from *l*-carvomenthylamine melted at 108.5–109.5° C. after similar treatment. Johnston and Read (7) report a melting point of 107° C. for this derivative.

Attempts to prepare the phenylurethane and the α-naphthylurethane resulted in mixtures of the derivative and the disubstituted urea, owing to the ease with which the respective carvomenthols underwent dehydration.

In fact, this process occurred so readily that it was observed during the fractionation of the respective carvomenthols. In each case a menthene fraction was collected in a trap which was chilled with a dry ice and acetone mixture. The product so obtained from carvomenthol prepared from *d*-carvomenthylamine had $d^{20°}$ = 0.8362, $n_D^{20°}$ = 1.4552, and $[\alpha]_D^{20°}$ = +19.54°; from it were prepared the nitrosochloride, which in an impure state melted at 81.5–83° C., and the nitrolbenzylamine base of the latter, m. p. 107–107.5° C., in agreement with the figure reported by Windemuth (1) for the derivative of an optically inactive carvomenthene.

The carvomenthene fraction collected during the fractionation of the carvomenthol prepared from *l*-carvomenthylamine had $d^{20°}$ = 0.8328, $n_D^{20°}$ = 1.4558, and $[\alpha]_D^{20°}$ = −10.98°. A nitrosochloride prepared from this product melted at 98–99° C.

Carvomenthene from Carvomenthol.—The respective carvomenthols were dehydrated by refluxing them over anhydrous cupric sulfate at 180–200° C. for 9 hrs., according to the method described by Richtmann and Kremers (8). The oily reaction product was then steam distilled and separated.

The carvomenthene thus prepared from the second largest fraction of carvomenthol derived from *d*-carvomenthylamine had $d^{21°}$ = 0.8246, $n_D^{20°}$ = 1.4585, and $[\alpha]_D^{23°}$ = +11.44°. It yielded a nitrosochloride, m. p. 90–91° C.; the nitrolbenzylamine base of the latter melted at 106–107° C. and its nitrolmorpholine base melted at 159–160° C. Windemuth (1) reports the melting point of the latter derivative as 155–156° C.

The carvomenthene which resulted from the dehydration of the second largest fraction of carvomenthol synthesized from *l*-carvomenthylamine had $d^{21°}$ = 0.8227, $n_D^{20°}$ = 1.4579, and $[\alpha]_D^{25°}$ = −8.65°. Its nitrosochloride melted at 90–91° C., and yielded a nitrolbenzylamine base, m. p. 107–107.5° C., and a nitrolmorpholine base, m. p. 159–160° C.

SUMMARY

1. The optically active carvomenthenes have been prepared from the isomeric carvoximes through a series of reactions.

2. In previous investigations on the carvone series, the work was carried out either on optically inactive substances or on only one of a pair of optical isomers.

3. No reports appear to exist in the literature concerning the fractionation of the isomeric carvomenthols under the high degree of vacuum employed in the present investigation. It is significant that dehydration of these alcohols should occur under the conditions observed.

4. The physical constants found for the compounds investigated were in general agreement with the reports of other workers. The chief difference occurred in the optical rotations, which varied with the nature of the starting materials.

5. The carvomenthenes obtained were opposite in optical sign from their respective sources, the isomeric carvoximes.

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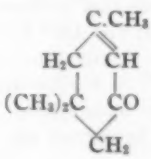
A Chemical Study of Isophorone and Some of Its Derivatives*

By Austin A. Dodge† and Edward Kremers‡

Isophorone, known also as isoacetophorone, is 1,1,3-trimethylcyclohexen-3-one-5; its structure may be represented as follows:



It appears to have been first prepared in 1859 by Fittig (1), who condensed acetone in the presence of caustic lime. It has since been prepared by other investigators (2, 3, 4, 5, 6, 7, 8, 9) from the same source through the use of other condensation agents.

It seemed desirable to attempt the preparation of an alcohol by the catalytic hydrogenation of the ketone, with the view of obtaining, by dehydration of the former, an unsaturated hydrocarbon. Such a hydrocarbon might be regarded, at least empirically, as a 9-carbon lower homologue of the 10-carbon *meta* terpenes.

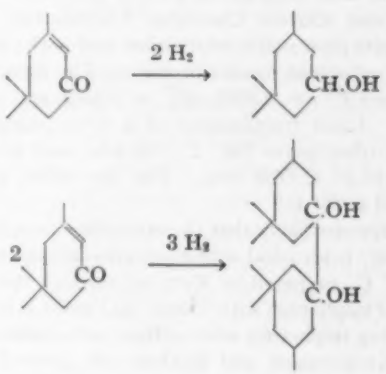
EXPERIMENTAL

The isophorone used in this investigation was supplied through the kindness of the Carbide and Carbon Chemicals Corporation. The product had the following constants: $d^{24°} = 0.9204$, $n_D^{20°} = 1.4778$. From it were prepared the oxime, m. p. 77–78° C., and the semicarbazone, m. p. 190–191° C. Numerous investigators have made varying reports of the respective melting points:

Oxime, M. P., °C.	Semicarbazone, M. P., °C.	Author
102	...	Tissier (2)
75–76; 99–100	...	Bredt and Rübel (3)
79–80	...	Kerp (4)
74–75	186	Knoevenagel and Fischer (10)
79–80	...	Wolff (7)
...	186	Knoevenagel and Blach (11)
78	190–191; 193	Crossley and Gilling (12)
78; 105–106	187; 191	Delacre (13)
74	186	Hess and Munderloh (9)

Hydrogenation Product of Isophorone.—Isophorone was hydrogenated over platinum black at room temperature in an apparatus manufactured by the Parr Instrument Company. The initial pressure used was about 38 lb./sq. in. The ratio of catalyst to isophorone was 2:35. The absorption of hydrogen corresponded to 2 moles. Usually the reduction product began to crystallize before the absorption of hydrogen was complete. The white crystalline product had a decidedly minty odor, was volatile, and tended to sublime in a stoppered container. After recrystallization from petroleum ether, the compound melted at 58.5–59° C. It was saturated toward bromine.

It is conceivable that the addition of hydrogen to isophorone might result either in the formation of the corresponding saturated alcohol or of the pinacol:



* Abstract of a thesis presented to the Graduate School of the University of Wisconsin in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1941.

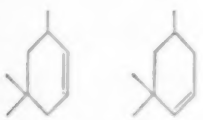
† Fritzsche Brothers Fellow in Pharmacy, University of Wisconsin, Madison, Wis., 1938–1941. Now Assistant Professor of Pharmacy, Philadelphia College of Pharmacy and Science, Philadelphia, Pa.

‡ Late Emeritus Professor of Pharmaceutical Chemistry, University of Wisconsin.

Molecular weight determinations by the cryoscopic method with benzene as solvent indicated that the compound was the secondary alcohol: calculated for $C_9H_{17}OH$, 142.2; found, 148.6.

The 3,5-dinitrobenzoate of the compound melted at 98.5–99° C. after several recrystallizations from alcohol. The acetate was obtained as an oily liquid, $d^{31°} = 0.9170$, $n_D^{26°} = 1.4385$.

The crystalline hydrogenation product was dehydrated according to the method described by Richtmann and Kremers (14). The oily reaction product was steam distilled and separated from the aqueous portion of the distillate. It possessed the following constants: $d^{24°} = 0.7933$, $n_D^{25°} = 1.4385$. Five cubic centimeters of the reaction product were fractionated; 2.2 cc. distilled below 131° C. and 2.3 cc. distilled at 131–135° C. The product was unsaturated toward bromine. It is possible that it may be identical with the 1,3,3-trimethylcyclohexene, b. p. 139–141° C./759 mm., $d_4^{23°} = 0.7981$, $n_D^{23°} = 1.4453$, prepared from trimethylcyclohexanol by Knoevenagel and Fischer (10). These authors advanced for their compound the following possibilities of structure:



They further pointed out that their compound might be identical with the "isogeraniolene" of Tiemann and Semmler (15), which had b. p. 138–140° C., $d^{22°} = 0.7978$, $n_D = 1.4434$, and to which the following structure was assigned by the latter authors:

Attempts to prepare the nitrosochloride and the nitrosite of the unsaturated hydrocarbon were unsuccessful. Further work will be necessary in order to characterize the compound.

Isophoronyl Alcohol.—Samples of a liquid substance labeled "isophoronyl alcohol" and of crystals bearing the same designation were supplied by the Carbide and Carbon Chemicals Corporation. Both products possessed a minty odor, and both appeared to be saturated toward bromine. The liquid product had $d^{25°} = 0.8908$, $n_D^{20°} = 1.4542$, and $[\alpha]_D = \pm 0°$. Upon fractionation of a 10-cc. sample, 4.4 cc. distilled below 194° C./739 mm., and 5.1 cc. at 194–194.5° C./739 mm. The crystalline product melted at 38° C.

It appears likely that the crystalline "isophoronyl alcohol" is identical with *trans*-dihydroisophorol, m. p. 37° C., prepared by Kerp (4) through the reduction of isophorone with sodium and moist ether. By reducing isophorone with sodium and absolute alcohol, Knoevenagel and Fischer (10) secured *trans*-dihydroisophorol, m. p. 34.5° C., and the *cis* form, b. p. 201–203° C./750 mm., $d_4^{19°} = 0.8906$, $d_4^{15°} = 0.9006$, $n_D^{15°} = 1.4550$. The latter constants agree quite closely with those observed for the liquid sample examined.

A molecular weight determination by the cryoscopic method made on the liquid sample gave a value of 156.4. Since it had been observed that the liquid deposited crystals upon chilling, a similar determination was made on these; the value found was 161.0.

In like manner, the molecular weight of the crystalline "isophoronyl alcohol" was found to be 164.1. All of these values are at variance with that demanded for $C_9H_{17}OH$, *viz.*, 142.

The 3,5-dinitrobenzoates of the respective "isophoronyl alcohols" were prepared; the derivative of the liquid product melted at 61.5–63° C., and that of the crystalline product melted at 71.5–72.5° C.

A sample of the liquid "isophoronyl alcohol" was dehydrated by refluxing it over potassium acid sulfate for 12 hrs. at 170–190° C. The oily reaction product was steam distilled and separated; it was found to have $d^{26°} = 0.8269$ and $n_D^{26°} = 1.4427$. The product was unsaturated toward bromine. Further work will be carried out on this substance in the future.

SUMMARY

1. Isophorone and two forms of "isophoronyl alcohol" (liquid and crystalline) supplied by the Carbide and Carbon Chemicals Corporation were examined. The oxime and semicarbazone of the former possessed melting points in general agreement with those recorded by earlier investigators.

2. A saturated secondary alcohol in crystalline form was obtained by the hydrogenation of isophorone over platinum black at room temperature. Its melting point differed from that of any reduction product of isophorone reported in the literature.

3. Compounds believed to be unsaturated hydrocarbons were prepared by the dehydration of the isophorone reduction product and of the liquid form of "isophoronyl alcohol." These products differed in their physical constants.

4. Since the 3,5-dinitrobenzoates of the isophorone reduction product and the two "isophoronyl alcohols" differed in their respective melting points, it would appear that three distinct compounds are represented. It is likely that the two "isophoronyl alcohols" are the *cis* and *trans* forms of dihydroisophorol.

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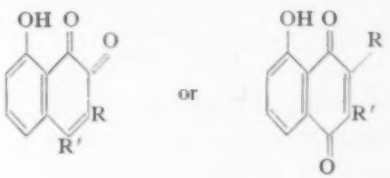
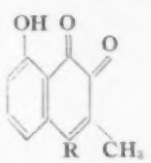
The Constitution of Celastrol, Part IV

*By Ole Gisvold**

In previous publications (1) it was shown that celastrol, a pigment found in the outer bark of the root of *Celastrus scandens*, has the formula $C_{22}H_{30}O_3$. It was postulated to be either a mono- or dialkyl substituted β- or α-naphthoquinone with one of the following tentative formulas, in which the sum of R and R′ equals $C_{12}H_{26}$.



Subsequent investigations on the constitution of this pigment indicate that it is a 3,4 - dialkyl - 8 - hydroxy - β - naphthoquinone. The alkyl group in position 3 appears to be a methyl group and the one in position 4, a homohydrogeranyl group ($-CH_2CH_2CH_2CH(CH_3)CH_2CH_2CH_2CH(CH_3)_2$), or possibly a hydrogeranyl group ($-CH_2CH_2CH(CH_3)CH_2CH_2CH_2CH(CH_3)_2$), as shown in the following formula:



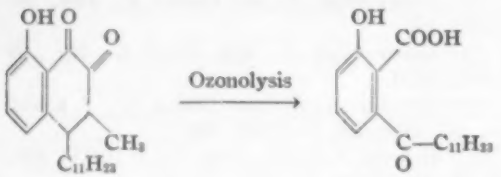
The evidence presented in this paper together with that of Fieser and Jones (2) clearly indicates that the pigment is definitely a substituted β-naphthoquinone. In a previous paper by the author (1), the solubility of celastrol in bisulfite was not carried out to the best advantage, as shown by Fieser. Also the very small amount of a derivative prepared by a reaction of methyl celastrol with *o*-phenylenediamine left room for doubt that it was an orthoquinone. The author has since tried to prepare a derivative with *o*-phenylenediamine and also with substituted hydrazines with negative results.

Previous oxidative studies yielded little if any satisfactory quantities of identifiable fragments. The most successful of this type of investigation was that carried out with cold permanganate.

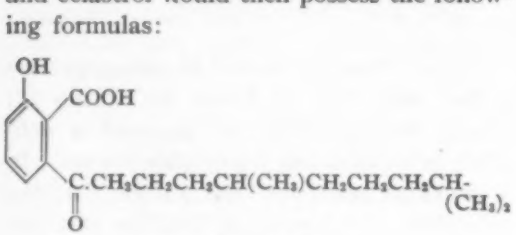
Samples of celastrol were ozonized in glacial acetic acid and the ozonide decomposed in the presence of hydrogen peroxide. This type of oxidative study yielded about 60% of an identifiable fragment; however, difficulty was encountered in attempting to purify the degradation product. The main degradation product responded to tests for a keto acid, but it failed to give a color reaction with ferric chloride. A 2,4-dinitrophenylhydrazone was readily obtained in a pure form suitable for analysis, the results of which corresponded to the formula $C_{25}H_{22}O_7N_4$, m. p. 192° C.

* Professor of Pharmaceutical Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota.

Celastrol therefore lost three carbon atoms upon ozonolysis and one could postulate the formation of a keto acid, as follows:



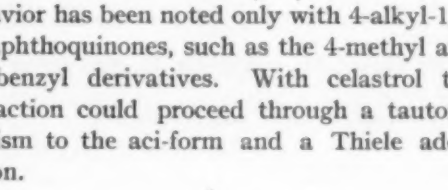
The keto acid obtained upon ozonolysis had a specific rotation in alcohol of +22.1. The optical activity therefore resides in the side chain $—C_{11}H_{23}$ and one could postulate that it is a homohydrogeranyl group, although the possibility of a hydrogeranyl group cannot be excluded. The keto acid and celastrol would then possess the following formulas:



Keto Acid

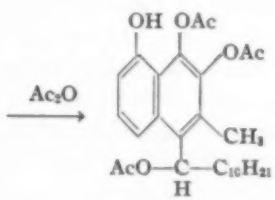
Celastrol

In a previous paper (1) it was reported that celastrol and methyl celastrol yielded yellow diacetates. These acetates were prepared by heating the substance in question with acetic anhydride and a relatively large quantity of pyridine. A continuation of acetylation studies has revealed some interesting observations. Sodium acetate and acetic anhydride yielded a colorless diacetate which turned yellow at the melting point, 241° C., which was the same as that of the previously prepared yellow diacetate. This colorless acetate turned yellow upon standing. In test acetylations, small amounts of pyridine gave a colorless acetylation mixture, whereas large amounts of pyridine gave a yellow acetylation mixture. Acetylation in the cold with acetic anhydride containing a trace of concentrated sulfuric acid (Thiele reagent) gave a permanently colorless abnormal triacetate which melted at 100–101° C. According to Fieser (3), quinones other than those having a conjugated system with hydrogen on the terminal carbon atom $(—CH=\underset{|}{C}—\underset{|}{C}=O)_1$, this behavior has been noted only with 4-alkyl-1,2-naphthoquinones, such as the 4-methyl and 4-benzyl derivatives. With celastrol the reaction could proceed through a tautomerism to the aci-form and a Thiele addition.



Celastrol

Celastrol (Aci-form)

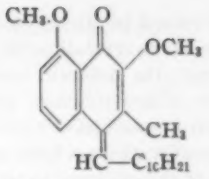


Celastrol Triacetate

The abnormal triacetate of methyl celastrol has also been prepared and found to be colorless.

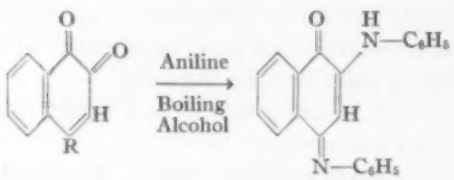
Fieser (4) has prepared the stable aci-form of certain β-naphthoquinones. Employing his technique an attempt was made to prepare the aci-form of celastrol. Celastrol was dissolved in cold concentrated sulfuric acid and after some time the deep red solution when poured into ice water yielded a yellow precipitate. A yellow solution was obtained when the precipitate was dissolved in ether, which indicated the presence of the aci-form. However, when attempts were made to crystallize this form the solution gradually assumed the characteristic red color of celastrol and no aci-form was isolated.

The aci-form of celastrol no doubt exists in the yellow dimethyl celastrol, a compound previously prepared (1) and reported. Its formula is shown as follows:



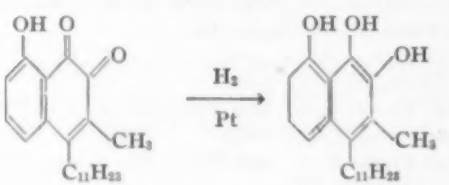
Dimethyl Celastrol

Fieser and Bradsher (5) have shown that the action of an excess of aniline in boiling alcohol on the 4-methyl, 4-benzyl, and 4-dicarbethoxy derivatives of 1,2-naphthoquinones resulted in each case with the displacement of the 4-substituent and formation of 2-anilino-1,4-naphthoquinone-4-anil. This substance was identical with the reaction product resulting from the interaction of β-naphthoquinone with aniline.



This reaction was carried out with celastrol with hopes that the alkyl group in position 4 in celastrol would be eliminated. This could aid in the characterization of this part of the molecule. However, celastrol was the only substance that could be recovered from the reaction mixture even after prolonged heating.

Reduction of celastrol in alcohol with platinum black as a catalyst yielded the corresponding phenol as dihydrocelastrol. Dihydrocelastrol crystallized as colorless needles from alcohol and melted at 177° C. In solution it was readily oxidized by air and even in the solid state it was slowly oxidized to the original quinone.



Celastrol Dihydrocelastrol

EXPERIMENTAL

Ozonolysis of Celastrol.—Five grams of celastrol were dissolved in 100 cc. of glacial acetic acid and the theoretical quantity of ozone passed through this solution at a low temperature.[1] The ozonide was decomposed by boiling in the presence of hydrogen peroxide. The solvent was removed under reduced pressure. The residue was taken up in ether, washed with water and the resulting solution evaporated to dryness. The residue thus obtained was extracted with hot petroleum ether. No detectable amount of material was soluble in petroleum ether. The residue weighed about 3 Gm. and was best purified by fractional crystallization from anhydrous ether and petroleum ether. The purest fraction was very pale yellow in color, melted at 166–167° C. and had a specific rotation of +22.1° in alcohol. It was soluble in sodium bicarbonate, formed a hydrazone, but gave no color test with ferric chloride. The substance is therefore a keto acid.

2,4-Dinitrophenylhydrazone of the Keto Acid.—This derivative was prepared by dissolving the above keto acid in alcohol, and sufficient solution of 2,4-dinitrophenylhydrazine (1.5% in 10% sulfuric acid containing 25% of alcohol) was added to equal about twice the theoretical quantity needed. Any turbidity encountered at this point was eliminated by the addition of alcohol. The mixture was heated on the steam bath for about 10 min. A small quantity of ether was added and the reaction mixture allowed to stand overnight. A crystalline brick-red hydrazone separated out. The derivative was collected on a fritted glass funnel, washed free from acid with water and then washed once each with alcohol and ether, m. p. 192° C. The derivative was soluble in alkali carbonate, giving a deep red solution.

Analysis ($C_{35}H_{32}O_7N_4$): Calcd.: C, 60.00; H, 6.40. Found: C, 59.81, 60.07; H, 6.36, 6.35.

ACETYLATION EXPERIMENTS

Thiele Reaction.—One gram of celastrol was dissolved in about 5 cc. of acetic acid to which was added one drop of concentrated sulfuric acid. The reaction mixture was allowed to stand overnight at room temperature during which time the solution became colorless. An excess of sodium acetate was added and the solvent removed under a vacuum. The residue was extracted with anhydrous ether and the colorless derivative fractionally crystallized from a mixture of anhydrous ether and petroleum ether. The purest fraction melted at 100–101° C. and analysis for acetyl value showed it to be an abnormal triacetate.

Analysis ($C_{23}H_{33}O_7$): Calcd.: CH_3CO, 26.4% (for 3 acetyl groups). Found: 28.0%.

The Thiele acetylation when applied to methyl celastrol also gave a colorless abnormal triacetate.

Analysis ($C_{29}H_{40}O_7$): Calcd.: CH_3CO, 25.7% (for 3 acetyl groups). Found: 24.8%.

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[1] By Dr. Hill, through the courtesy of Dr. Henne at Ohio State University.

The derivative is exceedingly easily hydrolyzed by dilute aqueous alkali in the cold and the solution quickly assumes an intense deep red color.

Acetylation with Sodium Acetate.—One-half gram of celastrol was acetylated by warming it on the steam bath for 1 hr. with an excess of acetic anhydride in the presence of sodium acetate. The mixture was allowed to stand overnight, after which time it became colorless. If the mixture was heated again it became yellow and upon cooling and standing it became colorless again. The excess reagent was removed by an air current in the hood. The residue was extracted with anhydrous ether, mixed with petroleum ether and the almost colorless derivative fractionally crystallized from this mixture. This acetate melted at 241° C., the same m. p. as that of the yellow acetate previously prepared and reported. This acetate although almost colorless turned deep yellow just before melting. Upon standing in a vial this acetate gradually turned a deep yellow.

Acetylation with Pyridine.—In test experiments, a small amount of pyridine in acetic anhydride gave a colorless solution with celastrol. However, when a large amount of pyridine was used, the reaction mixture assumed a deep yellow color.

Reaction with Aniline.—One gram of celastrol was dissolved in 15 cc. of warm absolute alcohol, 2 cc. of aniline was added and the solution was warmed on the steam bath for 1 hr. Upon standing and cooling, 0.5 Gm. of celastrol crystallized out. Further recovery of the reactants resulted only in the recovery of celastrol itself. These celastrol crystals were dark red in color. Prolonged heating of the reaction mixture gave the same results. Under the conditions of the above experiment, no reaction of celastrol with aniline takes place.

Reduction of Celastrol.—One-half gram of celastrol was reduced with platinum black in alcohol at 25° C. and 40 lbs. pressure. The reaction flask was removed, stoppered and allowed to stand for several weeks, after which time the reduction product separated as colorless clusters of fine needles which were quite insoluble in methyl and ethyl alcohols, ether, chloroform and petroleum ether. They were very soluble in pyridine; however, when in solution rapid oxidation took place and the solution soon became colored. Difficulty was experienced in separating the crystals from the platinum catalyst. Reduced celastrol melted at 177° C. Even in the solid state this reduction product, which could be called dihydrocelastrol (the reduced form of the quinone), was slowly oxidized by air to the orange quinone form.

Attempted Preparation of Aci-form of Celastrol.—One-half gram of celastrol was dissolved in 5 cc. of sulfuric acid at 0° C. and after 3 min. the deep red solution was poured into water. The yellow precipitate was dissolved in ether, washed with water and attempts made to crystallize the resulting product failed. That the aci-form was present was evidenced by the yellow solution, whereas an equal amount of celastrol would have made a red solution. Failure to crystallize the aci-form was due to the transformation of the aci-form to the quinone form during the process of attempted crystallization.

SUMMARY

1. Celastrol upon ozonolysis yields a keto acid which, according to the analysis of the 2,4-dinitrophenylhydrazone, has the formula $C_{19}H_{28}O_4$.

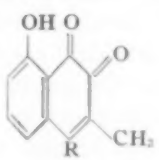
2. Celastrol forms a colorless abnormal triacetate characteristic of certain β-naphthoquinones when acetylated with the Thiele reagent.

3. Celastrol when acetylated with sodium acetate and acetic anhydride forms a colorless diacetate which turns deep yellow at the melting point or upon standing.

4. No reaction takes place with boiling alcohol and aniline.

5. Dihydrocelastrol, which is colorless, has been prepared in a crystalline form.

6. The evidence presented in this paper together with that of Fieser and Jones, (2) clearly indicates that celastrol is a 3,4-dialkyl-8-hydroxy-β-naphthoquinone with the following tentative formula, in which R may possibly be $-CH_2CH_2CH_2CH(CH_3)CH_2CH_2CH_2CH(CH_3)_2$ or $-CH_2CH_2CH(CH_3)CH_2CH_2CH_2CH(CH_3)_2$:



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The Heavy Metals Test for Volatile Oils*

By Frederick K. Bell and John C. Krantz, Jr.

Among the more comprehensive problems undertaken in connection with the preparation of the Twelfth Revision of the Pharmacopœia, the complete restudy of the heavy metals test for chemicals may be mentioned. As a result of this study the test has been placed on a quantitative basis and therefore brought into accord with the present-day procedures as commonly applied to reagent chemicals.

As a consequence of the authors' contacts with this problem, the desirability of placing the heavy metals test for the volatile oils on a similar basis seemed to be of sufficient importance to warrant investigation. It is the purpose of this paper to discuss some of the work that has been done and to describe a method of procedure.

There are twelve volatile oils for which a heavy metals test is required. These oils are: anise, bitter almond, chenopodium, cinnamon, clove, coriander, eucalyptus, fennel, juniper, orange, sassafras and wintergreen. Commercial samples of these oils with U. S. P. labeling were purchased in the open market and used in the present study.

The test of the U. S. P. XI reads as follows: "Shake 10 cc. of the oil with an equal volume of distilled water to which a drop of hydrochloric acid has been added, and pass hydrogen sulfide through the mixture until it is saturated: no darkening is produced in either the oil or the water (*lead or copper*)."

From the standpoint of simplicity there certainly can be no criticism of the test; but one might reasonably ask how accurately the presence or absence of darkening of the mixture can be determined particularly when no standard of comparison is provided. Such a standard might be obtained by passing an inert gas, such as nitrogen, through a similar oil and water mixture in the same manner as the hydrogen sulfide is passed through the test mixture. In this case, however, it might well be expected that color differences quite independent of any heavy metals effect might occur owing to the marked difference in reactivity of hydrogen sulfide and of nitrogen.

EXPERIMENTAL

In our search for an improved method we have tried several procedures bearing in mind the desirability of having a standardized method which could be applied to each of the oils. An obvious method depending upon the ashing of the oil sample has doubtlessly been extensively examined. Our experience with this method has led to unsatisfactory results. The ashing process is long and tedious and requires considerable skill and experience. Perhaps with a rather elaborate temperature control satisfactory and consistent results can be obtained. The method of wet ashing also received consideration including the conventional sulfuric and nitric acid mixture and also a number of other oxidizing agents. In every case, we were faced with the serious difficulty of the necessity of adding considerably more heavy metals, already present in the reagents required, than might be reasonably expected to be present in the oil itself.

We have found one method which seems to offer considerable promise and it will be described in some detail. In this method a water mixture of the oil to be examined is subjected to steam distillation until the oil is practically completely removed. The residual aqueous solution is then tested for heavy metals.

For the steam distillation we have used a very simple arrangement as shown in Fig. 1. A 500-cc. Pyrex flask which serves as the steam generator is equipped with a two-holed rubber stopper through which are passed a safety tube and a steam delivery tube which leads almost to the bottom of a 25- x 150-mm. Pyrex glass tube.

In carrying out the test, a steady stream of steam is generated. Obviously there must be no bumping in the generator. One gram of the oil to be tested is weighed into the test tube and 5 cc. of distilled water is added. The tube is then placed in the position shown in the figure and the distillation is allowed to proceed for 15 min. during which time gentle heat is applied to the test tube so as to prevent excessive condensation therein. At the end of this period the total volume of the liquid in the test tube should be 10 to 15 cc. In the case of some of the oils this liquid was quite clear and water-white while in others it showed more or less milkiness suggesting emulsifi-

* Received July 27, 1942, from the Department of Pharmacology, School of Medicine, University of Maryland, Baltimore, Md.

The work was performed as part of the program of revision of the United States Pharmacopœia.

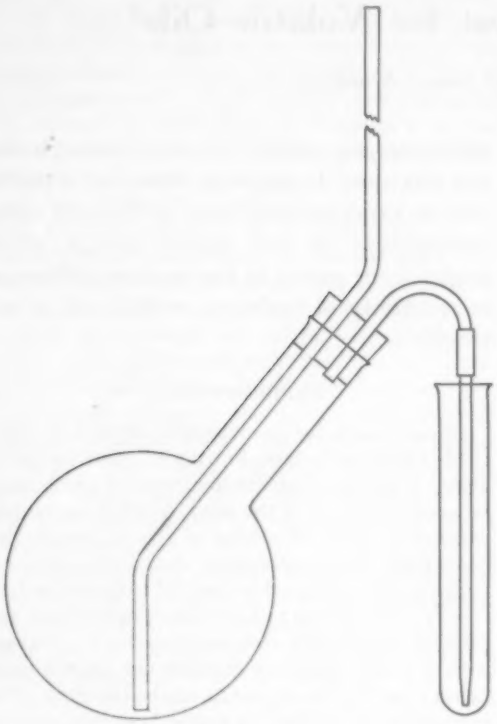

Fig. 1.

cation. Cloudy liquids are, of course, entirely unsuitable for the final step of the heavy metals test. In an effort to eliminate the formation of the cloudy residual solutions we have tried the addition of electrolytes to the water originally mixed with the oil sample. For example, 1 Gm. of sodium chloride was added to 5 cc. of the water before mixing with the oil. By this method no consistent improvement was obtained.

By the addition of one further step in the procedure we have been able to obtain clear and colorless residual solutions. The residual solution after the steam distillation is transferred to a separator, 25 cc. of ether is added and the mixture is extracted. The clear aqueous layer is separated and heated briefly on a steam bath until the ether is completely removed. The cooled solution is acidified by the addition of 1 cc. of 0.1 *N* hydrochloric acid and is then diluted to 25 cc. with distilled water.

This test solution is then treated with 10 cc. of hydrogen sulfide T. S. and after standing 10 min. its color is compared with that of 25 cc. of a standard aqueous solution containing 1 cc. of 0.1 *N* hydrochloric acid and the desired amount of lead as lead nitrate solution and to which has been added 10 cc. of hydrogen sulfide T. S. The two solutions are placed in similar comparator tubes and are observed by looking down through the tubes held above a white field. This portion of the test is identical with that of the heavy metals test for chemicals as adopted for the U. S. P. XII.

By means of this steam distillation method with subsequent ether extraction we have obtained consistently satisfactory results with ten of the twelve volatile oils previously listed. Even with numerous and extensive variations in the method we have been unable to adapt it to the oil of orange. Test solutions obtained from oil of sassafras, after the addition of the hydrogen sulfide, invariably became sufficiently tinted to obscure the final color comparison. Commercial U. S. P. samples of the other ten volatile oils were found to be below a ten parts per million heavy metals limit when examined by the proposed method. Some of the oils were found to be within a five parts per million limit. In each determination a comparison test was made in which ten parts per million of lead, as lead nitrate solution, was added to a 1-Gm. sample of the oil and then carried through the procedure outlined. An adequate recovery of this additional lead was consistently obtained, indicating that there is no appreciable loss in inorganic lead in the course of the procedure. Similar results were also obtained when copper, as copper sulfate solution, was employed as the added heavy metal.

We have experienced no difficulty in carrying out the test as proposed and recommend it as an improvement over the present test of the Pharmacopœia. With this recommendation, however, several points should be kept in mind. The heavy metal content of the volatile oils is to be attributed to one or both of two sources. Heavy metals may be present as a natural constituent of the original material and they may be introduced as contamination products during the processing of the oil. In either case, it is important to know if the heavy metals are present in organic combination and if such compounds are volatile with steam. Furthermore, if they are not appreciably volatile with steam they could be lost to the final test during the ether extraction step if sufficiently soluble in that solvent. The desirability of including oil of orange and oil of sassafras in any proposed method is fully recognized. Further work is being conducted along these lines.

SUMMARY

1. A procedure for the determination of heavy metals in volatile oils utilizing the principles of steam distillation has been described.

2. The method works quite satisfactorily for ten of the twelve volatile oils which require the test. Unsatisfactory results have been obtained with oil of orange and oil of sassafras.

3. All of the commercial U. S. P. oil samples examined in the course of the work gave a heavy metals test of less than ten parts per million.

A Color Test for Differentiating Barbaloin and Isobarbaloin and Identifying Different Varieties of Aloes*

By George L. Keenan and Llewellyn H. Welsh†

Collateral to a microcrystallographic study of barbaloin and isobarbaloin, commercial aloin constituents which are apparently isomeric, tests were made with a number of common microchemical reagents. None of the reagents employed gave significant results with the exception of a 5% aqueous solution of gold chloride. When a drop of this reagent was added to a small amount of isobarbaloin on a microscope slide, a distinct pink to red color was produced. Under the same conditions, barbaloin, prepared as described by Gardner and Joseph (1), gave merely a yellow solution. The red color with isobarbaloin occurred immediately at room temperature, and was intensified by gentle warming.

A number of chemical tests for differentiating varieties of aloes have appeared in the literature, and there have been described several reactions for differentiating isobarbaloin from barbaloin. The reactions which distinguish between the isomers appear to be based, usually, on the susceptibility of isobarbaloin to oxidation by such reagents as sodium nitrite-acetic acid (2) and cupric sulfate-sodium chloride (3). A rather extensive search of available literature failed to reveal any reference to the use of gold chloride solution for the purpose described in this paper, although the Eighth Revision of the United States Pharmacopœia includes an identification test for aloin in which the reagent produces a red coloration with the commercial drug. The test does not appear in the aloin monographs of subsequent revisions. Lenz (4) has observed that solutions of aloes "reducirten alkalische Kupferlösung und Goldlösung" on standing or heating, while Beal and Okey (5) refer to the use by Dragendorff[1] of gold chloride, as well as other reagents, in tests for aloes.

When the test was applied to different varieties of powdered aloes, distinctly different results were obtained for each: Curacao aloes gave an immediate red color, Cape specimens became green on standing and Socotrine samples remained brown. Several different commercial samples of each variety were tested. All specimens of commercial aloin which were tested gave the reddish color associated with isobarbaloin or Curacao aloes. The intensity of color given by Curacao aloes was much greater than that given by isobarbaloin—an indication that substances other than this compound present in the crude drug also produce the color. These substances appear to be concentrated in the aloin-free water-soluble fraction of the drug, since such a fraction, prepared by the method of Wirth, *et al.* (6), gave an intense red color with the reagent. Powdered specimens of senna leaf, cascara and buckthorn bark (*Rhamnus purshiana* and *R. frangula*), and rhubarb root failed to give the color. Tests were negative also with the following compounds: α-hydroxyanthraquinone-β-*d*-glucoside, aloe-emodin anthrone, α-hydroxyanthraquinone-β-*d*-arabinoside, β-hydroxyanthraquinone-β-*d*-glucoside and syringic acid. The last substance named, as might be expected, strongly reduced the reagent, forming a brown solution and black precipitate.

The test with gold chloride solution is simple in its application and is more convenient than the use of copper sulfate-sodium chloride combinations in aqueous or hydroalcoholic media (Klunge's reagent) (3) for the detection of isobarbaloin.

* Received November 2, 1942, from the U. S. Food and Drug Administration, Federal Security Agency, Washington, D. C.

† The authors wish to thank Dr. John H. Gardner of Washington University, St. Louis, Mo., for specimens of isobarbaloin, aloe-emodin anthrone and the hydroxyanthraquinone glycosides.

[1] The reference given by Beal and Okey (5) is not completely informative, but apparently refers to "Beiträge zur gerichtlichen Chemie einzelner organische Gifte," by G. Dragendorff, St. Petersburg (1872). This book, however, was found to be almost entirely concerned with alkaloids, and no work devoted to the anthraquinone drugs was detected therein.

SUMMARY

A color test has been described which employs gold chloride solution for identifying different varieties of aloes and for differentiating barbaloin and isobarbaloin. The test is simple in application and seems preferable to others which have appeared in the literature.

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Book Reviews

An Introduction to Materia Medica and Pharmacology, by HUGH ALISTER MCGUIGAN, Ph.D., M.D., and ELSIE E. KRUG, B.S., R.N. The C. V. Mosby Company, St. Louis, 1942. X + 779 pp., 83 figs., 14 x 22 cm. Price, $3.50.

A Textbook of Materia Medica, Pharmacology and Therapeutics, by HAROLD N. WRIGHT, M.S., Ph.D., and MILDRED MONTAG, R.N., M.A. W. B. Saunders Company, Philadelphia, 1942. 2nd Edition xvi + 647 pp., 93 figs., 13 x 19.5 cm. Price $3.00.

As sources of pharmacological information for pharmacists, both of these texts suffer from a paucity of detail concerning drug action. Because these volumes are intended for use as texts in Schools of Nursing, they present the material from the viewpoint of hospital routine and it is this feature that makes both books helpful to practitioners of Institutional Pharmacy. It is advantageous for any pharmacist to be conversant with hospital therapeutic practices and many pharmacists will wish to equip their professional libraries with these excellent compendia.

The McGuigan-Krug text represents the classical interpretation of pharmacology in a substantial manner and is essentially factual. There are times, however, when one wonders if the student of limited background in physiology is capable of interpreting the sketchy pharmacological reasoning. The discussion of the mode of action of atropine is a case in point. To one already familiar with the subject, the summary of proofs for the site of action of this drug is appreciated for its conciseness, but to the novitiate, the fact that under the influence of atropine, the eye is placed in autonomic imbalance in favor of the sympathetic system is not forcefully stated.

The documentation could have been materially improved by the addition of more primary source material, especially of the review type. The typography of the text is excellent and the use of tinted paper of the finest quality should be appreciated by the reader.

The fresh outlook of the Wright-Montag text is an achievement. Many teachers of pharmacology will wish to see this text for its exemplary pedagogy which more than compensates for its lack of detail. The authors see clearly the needs of the student of drug action as far as nursing is concerned and they have written with a consistent consciousness of that need. It is unfortunate that more elementary texts do not get away from the encyclopedic approach.

The many photographic illustrations are well conceived and splendidly executed. The schematic material expresses a viewpoint different from that ordinarily seen and all illustrative material is functional in character, tying in well with the text. The fact that the illustrative material is original contributes to the harmony between text and figure and is a welcome relief from the hackneyed illustrations that have been accompanying pharmacology texts for decades.

Teachers of pharmacy and pharmaceutical arithmetic can learn some excellent teaching methods in these fields from this text. The treatment of common fractions is well developed; and, although many will decry the childish presentation, a realist appreciates the necessity of clarifying a grade-school subject which is none too well understood by many college students.

This textbook is well documented with current literature and the typography is of the finest quality.—M. W. GREEN.

First Aid, Surgical and Medical, by WARREN H. COLE, M.D., F.A.C.S., and CHARLES B. PUESTOW, B.S., M.S., M.D., PH.D., F.A.C.S. D. Appleton Century Company, Inc., New York, 1942. xxiii + 351 pp., 92 figs., 14 x 22 cm. Price $3.00.

As a result of the war, colleges of pharmacy have recently laid increased stress upon the teaching of first aid and many teachers will be interested in new books in this field. The text by Cole and Puestow, although designed primarily for medical use, is quite adaptable to the needs of the pharmacy curriculum.

As one should expect, the greater portion of this text is given over to discussions of war casualties, but nevertheless considerable attention is paid to

civilian accidents. The terminology employed is technical without being so narrowly so that it cannot be understood by students with a limited background in the medical sciences. Sufficient anatomy and physiology are woven into the text to give a solid basis for the first aid measures employed. Wounds, burns, hemorrhage and shock are discussed in sufficient detail without becoming controversial, a factor which is highly important in the teaching of a subject as practical as first aid.

The chapter on "Gas and Bomb Raids" was written by Major H. C. Lueth and is based upon army information coupled with the experiences of the British. The discussions of aerial bombardment and bomb shock are especially noteworthy. Although the section on war gases is thorough, it suffers from a common fault of discussions of gas attack, *i. e.*, too much attention is given to the identification and treatment of individual gases at the expense of emphasis on the general principles of gas treatment and prevention. To the reviewer, it appears to be more logical to know a few simple, general directions for behavior during a gas attack than to be able to distinguish between Lewisite and mustard gas by their odors.

The collaborators are to be congratulated for the superb quality of the many line drawings which add much of practical value to the treatise.—M. W. GREEN.

Experiments in Organic Chemistry, by E. WERTHEIM. The Blakiston Company, Philadelphia, Pa., 1942. 221 pp., appendix, 23 x 16 cm. Price, $1.35.

This manual is designed to accompany the text, "Introductory Organic Chemistry," by the same author and to be used by students interested only in a short course in organic chemistry. The experiments are primarily of the "properties and tests" type. The more difficult preparations, especially those requiring less common apparatus and large quantities of chemicals and also time-consuming experiments, have not been included. It is well suited for classes where chemicals and apparatus are limited. The average time necessary to perform each experiment is given. Directions are fully and clearly given and figures and illustrations of apparatus assemblies and manipulations are exceptionally good. The manual contains 62 numbered experiments, is well indexed, and contains an appendix in which are included a table of the essential atomic weights, directions for emergency treatments, necessary chemicals listed by experiments, and directions for preparing special reagents. Questions are occasionally included in the text of the experiments and lists of questions are also appended. The craftsmanship is excellent for this type of book.—E. B. STARKEY.

Identification of Pure Organic Compounds, by ERNEST HAMLIN HUNTRESS, Ph.D., Assoc. Prof. of Organic Chemistry, Mass. Inst. of Tech., and SAMUEL PARSONS MULLIKEN, Ph.D., Late Prof. of Organic Chemistry, Mass. Inst. of Tech. John Wiley and Sons, Inc., New York, 1941. 691 pp., 15 x 23 cm. Price, $7.50.

The scope of this volume is limited to 1364 organic compounds selected from the large group of substances containing carbon and hydrogen or carbon, hydrogen and oxygen. Gases and compounds which do not have a melting point or definite boiling point, or are of a syrupy consistency, are excluded. A comparison of this volume with Mulliken's original "Indentification of Pure Organic Compounds" shows the deletion of many compounds of lesser importance and the inclusion of many substances now well known and commercially available which were formerly merely laboratory curiosities.

This edition introduces two new features. An index of chemical type has been placed at the opening of each chapter to facilitate rapid location of chemical compounds. An index containing tables of melting points of compounds and their derivatives arranged in a sequence of increasing temperature is given in Chapter XIII. All of the melting points found in the body of the book are classified and summarized in this chapter.

Compounds are classified by a method based upon chemical rather than physical properties and amply described in the first chapter. Each compound for which data are given has an arbitrary number consisting of a digit representing the order, followed by a colon and an arbitrary four digit number indicating the specific compound. Thus, all compounds of this book have the number "one" for the single digit. The system is analogous to a telephone number in which the single digit corresponds to the exchange and the four digits, the individual line. All compounds in the general index of the book are located by this number system rather than by the customary page reference.

Chapter II describes the common generic tests for the nine genuses: (1) aldehydes, (2) carbohydrates, (3) acids, (4) phenolic compounds, (5) esters, (6) anhydrides and lactones, (7) ketones, (8) alcohols, (9) hydrocarbons, ethers, etc. Each genus is separately described in succeeding chapters in such a way that the qualitative identity of an "unknown" is easily established. The pertinent facts regarding each compound listed are: the name or names of the compound, structural formula, empirical formula, Beilstein number, physical properties, general information and properties and reactions, preliminary tests, derivatives, and literature references. All of the reactions cited have actually been carried out by the author, a valuable and almost unique contribution.

The reviewer has had numerous occasions to refer to this volume and can attest its applicability. Any library will be enriched by the possession of this book of general reference. For classroom use, it presents a technique for identifying organic compounds in a systematic manner, teaching the student a methodic approach to qualitative organic

analysis which will be useful to him on many occasions.—EMERSON C. BEELER.

The Chemistry and Manufacture of Cosmetics, by MAISON G. DE NAVARRE. D. Van Nostrand Company, 250 Fourth Avenue, New York, 1941. xix + 745 pp., 180 figs., 15.5 x 23 cm. Price, $8.00.

This book departs from most of the other texts on cosmetology in that it aims not to be purely a formulary, but rather a unified guide to the principles behind the formulas. These principles are laid down in such a manner that they are of value to both small and large operators, a factor that will appeal to many pharmacists.

The book is divided into 10 parts of 34 chapters. The main parts are: weights and measures; types of equipment for small manufacture and properties of raw materials; a resumé of fundamental principles; preservatives and antioxidants; cosmetic colors; emulsions; formulary of the principal types of cosmetics; physiology of the skin, hair and scalp; regulations and interpretations of the Federal Food, Drug, and Cosmetic Act; and appendix and bibliography.

Although most of the fundamental material is well known to practicing pharmacists and teachers of pharmacy, the author frequently treats the material in a novel way which makes it most illuminating. It is quite apparent that the aim of the author is to be practical at all times but not at the expense of fundamental principles. The discussions and the tabulations of properties of raw materials are also presented in a most helpful manner. The table of physical properties of acceptable cosmetic colors is of special value, and its use can no doubt be expanded beyond the purely cosmetic one.

Part VII, which deals with type preparations, gives many formulas for the various types of cosmetics such as creams, powders, make-up, etc. But, while the formulas as set up are satisfactory, it is intended that they be used as a guide for further development in order to obtain a distinctive product.

The section on the physiology of the skin, hair and scalp is rather scanty, but in the light of the paucity of information on skin pharmacology at the moment, it is probably well that the author is not too dogmatic. The section on dentifrices is well written, the author having been mindful of the position of the American Dental Association with regard to the limitations of this economically important class of substances.

The portion dealing with the Food, Drug, and Cosmetic Act is written by Attorney Ralph J. Mill. Not only are the salient features of the Law, as it applies to cosmetics, well stated, but the interpretations will no doubt help many through the maze of Federal rulings.

The documentation appears to be fair and the list of patents will no doubt be helpful. Technically, the book is well written and printed on a good quality paper and exhibits careful workmanship throughout. It is gratifying to see that the stimulus for this book arises from pharmaceutical needs and it is to be hoped that other problems peculiar to our field will find such a concrete answer.—E. C. BEELER.

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SUMMARY

A color test has been described which employs gold chloride solution for identifying different varieties of aloes and for differentiating barbaloin and isobarbaloin. The test is simple in application and seems preferable to others which have appeared in the literature.

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Book Reviews

An Introduction to Materia Medica and Pharmacology, by HUGH ALISTER MCGUIGAN, Ph.D., M.D., and ELSIE E. KRUG, B.S., R.N. The C. V. Mosby Company, St. Louis, 1942. X + 779 pp., 83 figs., 14 x 22 cm. Price, $3.50.

A Textbook of Materia Medica, Pharmacology and Therapeutics, by HAROLD N. WRIGHT, M.S., Ph.D., and MILDRED MONTAG, R.N., M.A. W. B. Saunders Company, Philadelphia, 1942. 2nd Edition xvi + 647 pp., 93 figs., 13 x 19.5 cm. Price $3.00.

As sources of pharmacological information for pharmacists, both of these texts suffer from a paucity of detail concerning drug action. Because these volumes are intended for use as texts in Schools of Nursing, they present the material from the viewpoint of hospital routine and it is this feature that makes both books helpful to practitioners of Institutional Pharmacy. It is advantageous for any pharmacist to be conversant with hospital therapeutic practices and many pharmacists will wish to equip their professional libraries with these excellent compendia.

The McGuigan-Krug text represents the classical interpretation of pharmacology in a substantial manner and is essentially factual. There are times, however, when one wonders if the student of limited background in physiology is capable of interpreting the sketchy pharmacological reasoning. The discussion of the mode of action of atropine is a case in point. To one already familiar with the subject, the summary of proofs for the site of action of this drug is appreciated for its conciseness, but to the novitiate, the fact that under the influence of atropine, the eye is placed in autonomic imbalance in favor of the sympathetic system is not forcefully stated.

The documentation could have been materially improved by the addition of more primary source material, especially of the review type. The typography of the text is excellent and the use of tinted paper of the finest quality should be appreciated by the reader.

The fresh outlook of the Wright-Montag text is an achievement. Many teachers of pharmacology will wish to see this text for its exemplary pedagogy which more than compensates for its lack of detail. The authors see clearly the needs of the student of drug action as far as nursing is concerned and they have written with a consistent consciousness of that need. It is unfortunate that more elementary texts do not get away from the encyclopedic approach.

The many photographic illustrations are well conceived and splendidly executed. The schematic material expresses a viewpoint different from that ordinarily seen and all illustrative material is functional in character, tying in well with the text. The fact that the illustrative material is original contributes to the harmony between text and figure and is a welcome relief from the hackneyed illustrations that have been accompanying pharmacology texts for decades.

Teachers of pharmacy and pharmaceutical arithmetic can learn some excellent teaching methods in these fields from this text. The treatment of common fractions is well developed; and, although many will decry the childish presentation, a realist appreciates the necessity of clarifying a grade-school subject which is none too well understood by many college students.

This textbook is well documented with current literature and the typography is of the finest quality.—M. W. GREEN.

First Aid, Surgical and Medical, by WARREN H. COLE, M.D., F.A.C.S., and CHARLES B. PUESTOW, B.S., M.S., M.D., PH.D., F.A.C.S. D. Appleton Century Company, Inc., New York, 1942. xxiii + 351 pp., 92 figs., 14 x 22 cm. Price $3.00.

As a result of the war, colleges of pharmacy have recently laid increased stress upon the teaching of first aid and many teachers will be interested in new books in this field. The text by Cole and Puestow, although designed primarily for medical use, is quite adaptable to the needs of the pharmacy curriculum.

As one should expect, the greater portion of this text is given over to discussions of war casualties, but nevertheless considerable attention is paid to

civilian accidents. The terminology employed is technical without being so narrowly so that it cannot be understood by students with a limited background in the medical sciences. Sufficient anatomy and physiology are woven into the text to give a solid basis for the first aid measures employed. Wounds, burns, hemorrhage and shock are discussed in sufficient detail without becoming controversial, a factor which is highly important in the teaching of a subject as practical as first aid.

The chapter on "Gas and Bomb Raids" was written by Major H. C. Lueth and is based upon army information coupled with the experiences of the British. The discussions of aerial bombardment and bomb shock are especially noteworthy. Although the section on war gases is thorough, it suffers from a common fault of discussions of gas attack, *i. e.*, too much attention is given to the identification and treatment of individual gases at the expense of emphasis on the general principles of gas treatment and prevention. To the reviewer, it appears to be more logical to know a few simple, general directions for behavior during a gas attack than to be able to distinguish between Lewisite and mustard gas by their odors.

The collaborators are to be congratulated for the superb quality of the many line drawings which add much of practical value to the treatise.—M. W. GREEN.

Experiments in Organic Chemistry, by E. WERTHEIM. The Blakiston Company, Philadelphia, Pa., 1942. 221 pp., appendix, 23 x 16 cm. Price, $1.35.

This manual is designed to accompany the text, "Introductory Organic Chemistry," by the same author and to be used by students interested only in a short course in organic chemistry. The experiments are primarily of the "properties and tests" type. The more difficult preparations, especially those requiring less common apparatus and large quantities of chemicals and also time-consuming experiments, have not been included. It is well suited for classes where chemicals and apparatus are limited. The average time necessary to perform each experiment is given. Directions are fully and clearly given and figures and illustrations of apparatus assemblies and manipulations are exceptionally good. The manual contains 62 numbered experiments, is well indexed, and contains an appendix in which are included a table of the essential atomic weights, directions for emergency treatments, necessary chemicals listed by experiments, and directions for preparing special reagents. Questions are occasionally included in the text of the experiments and lists of questions are also appended. The craftsmanship is excellent for this type of book.—E. B. STARKEY.

Identification of Pure Organic Compounds, by ERNEST HAMLIN HUNTRESS, Ph.D., Assoc. Prof. of Organic Chemistry, Mass. Inst. of Tech., and SAMUEL PARSONS MULLIKEN, Ph.D., Late Prof. of Organic Chemistry, Mass. Inst. of Tech. John Wiley and Sons, Inc., New York, 1941. 691 pp., 15 x 23 cm. Price, $7.50.

The scope of this volume is limited to 1364 organic compounds selected from the large group of substances containing carbon and hydrogen or carbon, hydrogen and oxygen. Gases and compounds which do not have a melting point or definite boiling point, or are of a syrupy consistency, are excluded. A comparison of this volume with Mulliken's original "Indentification of Pure Organic Compounds" shows the deletion of many compounds of lesser importance and the inclusion of many substances now well known and commercially available which were formerly merely laboratory curiosities.

This edition introduces two new features. An index of chemical type has been placed at the opening of each chapter to facilitate rapid location of chemical compounds. An index containing tables of melting points of compounds and their derivatives arranged in a sequence of increasing temperature is given in Chapter XIII. All of the melting points found in the body of the book are classified and summarized in this chapter.

Compounds are classified by a method based upon chemical rather than physical properties and amply described in the first chapter. Each compound for which data are given has an arbitrary number consisting of a digit representing the order, followed by a colon and an arbitrary four digit number indicating the specific compound. Thus, all compounds of this book have the number "one" for the single digit. The system is analogous to a telephone number in which the single digit corresponds to the exchange and the four digits, the individual line. All compounds in the general index of the book are located by this number system rather than by the customary page reference.

Chapter II describes the common generic tests for the nine genuses: (1) aldehydes, (2) carbohydrates, (3) acids, (4) phenolic compounds, (5) esters, (6) anhydrides and lactones, (7) ketones, (8) alcohols, (9) hydrocarbons, ethers, etc. Each genus is separately described in succeeding chapters in such a way that the qualitative identity of an "unknown" is easily established. The pertinent facts regarding each compound listed are: the name or names of the compound, structural formula, empirical formula, Beilstein number, physical properties, general information and properties and reactions, preliminary tests, derivatives, and literature references. All of the reactions cited have actually been carried out by the author, a valuable and almost unique contribution.

The reviewer has had numerous occasions to refer to this volume and can attest its applicability. Any library will be enriched by the possession of this book of general reference. For classroom use, it presents a technique for identifying organic compounds in a systematic manner, teaching the student a methodic approach to qualitative organic

analysis which will be useful to him on many occasions.—EMERSON C. BEELER.

The Chemistry and Manufacture of Cosmetics, by MAISON G. DE NAVARRE. D. Van Nostrand Company, 250 Fourth Avenue, New York, 1941. xix + 745 pp., 180 figs., 15.5 x 23 cm. Price, $8.00.

This book departs from most of the other texts on cosmetology in that it aims not to be purely a formulary, but rather a unified guide to the principles behind the formulas. These principles are laid down in such a manner that they are of value to both small and large operators, a factor that will appeal to many pharmacists.

The book is divided into 10 parts of 34 chapters. The main parts are: weights and measures; types of equipment for small manufacture and properties of raw materials; a resumé of fundamental principles; preservatives and antioxidants; cosmetic colors; emulsions; formulary of the principal types of cosmetics; physiology of the skin, hair and scalp; regulations and interpretations of the Federal Food, Drug, and Cosmetic Act; and appendix and bibliography.

Although most of the fundamental material is well known to practicing pharmacists and teachers of pharmacy, the author frequently treats the material in a novel way which makes it most illuminating. It is quite apparent that the aim of the author is to be practical at all times but not at the expense of fundamental principles. The discussions and the tabulations of properties of raw materials are also presented in a most helpful manner. The table of physical properties of acceptable cosmetic colors is of special value, and its use can no doubt be expanded beyond the purely cosmetic one.

Part VII, which deals with type preparations, gives many formulas for the various types of cosmetics such as creams, powders, make-up, etc. But, while the formulas as set up are satisfactory, it is intended that they be used as a guide for further development in order to obtain a distinctive product.

The section on the physiology of the skin, hair and scalp is rather scanty, but in the light of the paucity of information on skin pharmacology at the moment, it is probably well that the author is not too dogmatic. The section on dentifrices is well written, the author having been mindful of the position of the American Dental Association with regard to the limitations of this economically important class of substances.

The portion dealing with the Food, Drug, and Cosmetic Act is written by Attorney Ralph J. Mill. Not only are the salient features of the Law, as it applies to cosmetics, well stated, but the interpretations will no doubt help many through the maze of Federal rulings.

The documentation appears to be fair and the list of patents will no doubt be helpful. Technically, the book is well written and printed on a good quality paper and exhibits careful workmanship throughout. It is gratifying to see that the stimulus for this book arises from pharmaceutical needs and it is to be hoped that other problems peculiar to our field will find such a concrete answer.—E. C. BEELER.

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